30700

National Library of Canada / Bibliothèque nationale du Canada

CANADIAN THESES ON MICROFICHE / THÈSES CANADIENNES SUR MICROFICHE

NAME OF AUTHOR/*NOM DE L'AUTEUR* Wayne Bruce Hay

TITLE OF THESIS/*TITRE DE LA THÈSE* Effect of Downstream Resistance on Pressure Drop Across Minor Stenoses

UNIVERSITY/*UNIVERSITÉ* University of Alberta

DEGREE FOR WHICH THESIS WAS PRESENTED/*GRADE POUR LEQUEL CETTE THÈSE FUT PRÉSENTÉE* Master of Science

YEAR THIS DEGREE CONFERRED/*ANNÉE D'OBTENTION DE CE GRADE* 1976

NAME OF SUPERVISOR/*NOM DU DIRECTEUR DE THÈSE* Dr. K. J. Hutchison

Permission is hereby granted to the NATIONAL LIBRARY OF CANADA to microfilm this thesis and to lend or sell copies of the film.

The author reserves other publication rights, and neither the thesis nor extensive extracts from it may be printed or otherwise reproduced without the author's written permission.

L'autorisation est, par la présente, accordée à la BIBLIOTHÈQUE NATIONALE DU CANADA de microfilmer cette thèse et de prêter ou de vendre des exemplaires du film.

L'auteur se réserve les autres droits de publication; ni la thèse ni de longs extraits de celle-ci ne doivent être imprimés ou autrement reproduits sans l'autorisation écrite de l'auteur.

DATED/*DATÉ* Oct 18, 1976 SIGNED/*SIGNÉ* Wayne Hay

PERMANENT ADDRESS/*RÉSIDENCE FIXE* #202, 10959-102St.
Edmonton, Alta

NL-91 (3-74)

INFORMATION TO USERS

THIS DISSERTATION HAS BEEN MICROFILMED EXACTLY AS RECEIVED

This copy was produced from a microfiche copy of the original document. The quality of the copy is heavily dependent upon the quality of the original thesis submitted for microfilming. Every effort has been made to ensure the highest quality of reproduction possible.

PLEASE NOTE: Some pages may have indistinct print. Filmed as received.

Canadian Theses Division
Cataloguing Branch
National Library of Canada
Ottawa, Canada K1A ON4

AVIS AUX USAGERS

LA THESE A ETE MICROFILMEE TELLE QUE NOUS L'AVONS RECUE

Cette copie a été faite à partir d'une microfiche du document original. La qualité de la copie dépend grandement de la qualité de la thèse soumise pour le microfilmage. Nous avons tout fait pour assurer une qualité supérieure de reproduction.

NOTA BENE: La qualité d'impression de certaines pages peut laisser à désirer. Microfilmee telle que nous l'avons reçue.

Division des thèses canadiennes
Direction du catalogage
Bibliothèque nationale du Canada
Ottawa, Canada K1A ON4

THE UNIVERSITY OF ALBERTA

EFFECT OF DOWNSTREAM RESISTANCE ON THE PRESSURE DROP ACROSS MINOR STENOSES

by

© Wayne Bruce Hay

A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES AND RESEARCH

IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE

OF MASTERS OF SCIENCE

DEPARTMENT OF PHYSIOLOGY

EDMONTON, ALBERTA

FALL, 1976

THE UNIVERSITY OF ALBERTA

FACULTY OF GRADUATE STUDIES AND RESEARCH

The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research, for acceptance, a thesis entitled EFFECT OF DOWNSTREAM RESISTANCE ON THE PRESSURE DROP ACROSS MINOR STENOSES submitted by WAYNE BRUCE HAY in partial fulfilment of the requirements for the degree of Master of Science.

.....
Supervisor

.....

.....

.....

.....

.....

Date 12th Oct 1976

ABSTRACT

Investigations have shown that under resting conditions in vivo little change in blood flow or pressure drop is caused until the cross-sectional area of the vessel has been reduced by a "critical" amount of about 80%. Further investigations have shown that the shape, number and sequence of stenoses affect the blood flow and pressure drop to only a minor degree. Changes in the peripheral vascular resistance, however, have been shown to alter the level of "critical" stenosis.

The investigations described herein were designed to study the effect of downstream resistance on the pressure drop across minor stenoses, i.e. those that do not cause significant pressure drop under resting downstream (peripheral) resistance. It further deals with the question of whether a decrease in peripheral vascular resistance can increase the pressure drop across minor stenoses with the secondary effect of the increase in blood flow eliminated.

Constant pressure and constant flow experiments were performed initially on rigid acrylic models of stenoses to discover what degree of constriction with what magnitude of downstream resistance produces significant pressure and flow reduction. There was no appreciable pressure drop across the stenosis until the resistance across the stenosis was a significant part of the total resistance (i.e. stenosis plus downstream resistance). It was shown that with very low downstream resistance there may be a significant pressure drop across a 53% stenosis. In the constant flow model experiments if the down-

stream resistance was changed but the flow rate was kept constant there was no increase in the pressure drop across the stenosis. Therefore, for the model experiments, the increase in pressure drop with decreased downstream resistance was caused by the increased flow.

The results of the model studies suggested the possibility that a stenosis which produces little pressure drop under conditions of high downstream resistance may produce significant pressure reduction under conditions of lowered downstream resistance. The effect of changes in downstream resistance caused by the intra-arterial administration of vasodilator substances (histamine, isoproterenol or acetylcholine) on the pressure drop across minor stenoses placed on the dog thoracic aorta in vivo were examined. It was found that a decrease in downstream resistance increased the blood flow and increased the pressure drop across the stenosis.

The results of the aorta experiments showed that a decrease in downstream resistance increases the pressure drop across a stenosis, but this was accomplished with an increase in blood flow. To separate the increase in flow rate from the decrease in downstream vascular resistance the perfused dog hind limb was employed. This enabled the blood flow to be held constant during the intra-arterial infusion of a vasodilator substance (acetylcholine). With this constant flow set-up there was no increase in pressure drop across the stenosis when the downstream vascular resistance was decreased. It was concluded that the increase in pressure drop across a stenosis elicited by changes in vascular resistance are accounted for by changes in blood flow.

ACKNOWLEDGEMENTS

To my supervisor, Dr. K.J. Hutchison, I am greatly thankful for his guidance and assistance. The technical assistance of Mr. Darryl O'Brien is appreciated. The assistance and cooperation received from various members of the Department of Physiology in the preparation of this thesis is appreciated. I am grateful to the Alberta Heart Foundation for helping fund the research.

TABLE OF CONTENTS

	PAGE
GENERAL INTRODUCTION	1
SECTION I: Effect of Changes in Downstream Resistance on Pressures and Flow about Stenoses - Model Studies	13
1. Introduction	14
2. Materials and Methods	15
3. Results	
A. Pressure Profiles - Constant Pressure Experiments	19
B. Pressure-Flow Characteristics - Constant Flow Experiments	26
C. Pressure Drop - Constant Pressure and Constant Flow Experiments	32
4. Discussion	36
SECTION II: Effect of Changes in Vascular Resistance and Blood Flow on the Pressure Drop Across Minor Stenoses Placed on the Dog Thoracic Aorta	40
1. Introduction	41
2. Materials and Methods	43
3. Results	
A. Vasodilation by Infusions of Histamine	46
B. Vasodilation by Infusions of Isoproterenol ...	49
C. Vasodilation by Infusions of Acetylcholine ...	52
4. Discussion	55
SECTION III: Effect of Changes in Vascular Resistance on the Pressure Drop Across Minor Stenoses Placed on the Perfused Dog Ileo-Femoral Artery	59
1. Introduction	60
2. Materials and Methods	62

3. Results 66

4. Discussion 69

SUMMARY 71

BIBLIOGRAPHY 73

LIST OF TABLES

TABLE		PAGE
I	Slopes of upstream pressure versus flow of Figure 6	28
II	Slopes of downstream pressure versus flow of Figure 7	31
III	Effect of intra-arterial infusions of histamine on upstream pressure, pressure drop, flow and downstream vascular resistance under control conditions and with 50%, 70% and 80% stenoses applied to the dog thoracic aorta	47a
IV	Effect of intra-arterial infusions of isoproterenol on upstream pressure, pressure drop, flow and downstream vascular resistance under control conditions and with a 70% stenosis applied to the dog thoracic aorta	50a
V	Effect of intra-arterial infusions of acetylcholine on upstream pressure, pressure drop, flow and downstream vascular resistance under control conditions and with a 70% stenosis applied to the dog thoracic aorta	53a
VI	Response of the perfused dog hind limb to intra-arterial infusions of acetylcholine under control conditions and with stenoses applied	67a

LIST OF FIGURES

FIGURE		PAGE
1.	Schematic diagram of acrylic model	16
2.	Pressure profiles across a 53% stenosis	20
3.	Pressure profiles across a 75% stenosis	22
4.	Pressure profiles across a 89% stenosis	23
5.	Pressure profiles across a 97% stenosis	25
6.	Effect of flow, % stenosis and downstream resistance on upstream pressure	27
7.	Effect of flow, % stenosis and downstream resistance on downstream pressure	30
8.	Effect of flow on pressure drop across 53%, 75%, 89% and 97% stenoses	33
9.	Schematic illustration of preparation for the experiments on the dog thoracic aorta in vivo	44
10.	Effect of intra-arterial infusions of histamine on upstream pressure, pressure drop, flow and downstream vascular resistance and with a 0%, 50%, 70% or 80% stenosis applied to the dog thoracic aorta	47
11.	Effect of intra-arterial infusions of isoproterenol on upstream pressure, pressure drop, flow and downstream vascular resistance with a 0% or 70% stenosis applied to the dog thoracic aorta	50
12.	Effect of intra-arterial infusions of acetylcholine on upstream pressure, pressure drop, flow and downstream vascular resistance with a 0% or 70% stenosis applied to the dog thoracic aorta	53
13.	Illustration of preparation for the experiments on the perfused dog ileo-femoral artery	63
14.	Response of the perfused dog hind limb to intra-arterial infusions of acetylcholine with and without stenoses applied to the femoral artery	67

GENERAL INTRODUCTION

Many aspects of an arterial stenosis (i.e. a localized constriction of an artery) have been studied. Stenoses have been observed to have effects on blood flow and pressure. Furthermore, the length, shape and number of stenoses, as well as the downstream resistance, can effect the pressure-flow relationships about the stenosis.

The effect of an arterial stenosis on blood flow through the carotid, aortic, iliac, femoral and other arteries, such as the renal, has been investigated. Under resting conditions in vivo little change in blood flow is caused until the cross-sectional area of the vessel has been reduced by a "critical" amount of about 80%.

Studies on the effect of a stenosis on the blood flow in the carotid artery have shown that severe arterial stenoses were necessary to reduce blood flow. In 1938 Mann et al[1] showed that an 8 mm long stenosis placed around the outside of the canine carotid artery caused no change in blood flow even though the area of the lumen was decreased 50%. A reduction in lumen area of 90% was necessary to produce a 50% reduction in blood flow. Also employing the dog carotid artery Vondruden et al (1964)[2] demonstrated that with stenoses causing 75%, 86%, 94% and 98% reduction in cross-sectional area that blood flow was maintained at 85%, 70%, 40% and 15% of the normal blood flow for the respective stenoses. Eklof and Schwartz (1970)[3] determined that the "critical" stenosis for the canine carotid artery was 81% at which level a 15% reduction in flow occurred. Employing the common carotid artery of the monkey Youmans and Kindt (1968)[4] found it was necessary to reduce the cross-sectional area by 90% before a significant decrease in blood flow occurred. The above studies show that for

the carotid artery the cross-sectional area must be reduced by 80 to 90% before a significant decrease in blood flow occurs.

The effect of a stenosis on blood flow in the aorta is insignificant unless the constriction is very severe. In 1953 Wylie and McGuiness[5] studied the effects of aortic and iliac arterial stenosis on blood flow and observed that at least 90% of the arterial lumen had to be occluded before blood flow reduction was sufficient to cause symptoms. Haimovici and Echer (1956)[6], however, found that a critical point of about 82% reduction in cross-sectional area of the lumen was necessary before significant manifestation of blood flow impairment was present. They had investigated 13 patients with aortoiliac stenosis. In 1961 Schenk et al[7] placed marked constrictions on the descending aorta just distal to the subclavian artery in large adult dogs and observed that flow through the constricted area remained remarkably high in spite of a 94% reduction in the cross-sectional area. In 1969 Kindt and Youmans[8] found, using a stricture of short length on the dog abdominal aorta, that a significant decrease in flow does not occur until the stricture reduces the area by 90% or more. Most of the studies above show that for the aorta the cross-sectional area must be reduced by at least 90% before a significant decrease in blood flow occurs.

Studies on the iliac and femoral arteries have shown that the cross-sectional area of these arteries must be reduced by about 80% before a significant decrease in blood flow occurs. In 1963 May et al [9,10] found that in the resting dog it was necessary to constrict the luminal area of the iliac artery by 80% before a significant 20%

decrease in arterial flow occurred. Beyond this degree of stenosis the reduction in flow with added increments of constriction were precipitous. They termed the 80% stenosis to be "critical". In 1964 Van de Berg et al[11] found that under resting conditions the "critical" stenosis of the dog femoral-iliac artery was 82%. Therefore the cross-sectional area of the iliac and femoral arteries must be reduced by about the same amount as the carotid, i.e. 80%, before a significant reduction in blood flow occurs.

Studies performed on other arteries have confirmed the fact that severe constriction of an artery, under resting conditions, is necessary to significantly reduce blood flow. In 1959 Page et al[12] in dealing with the mechanisms, diagnosis and treatment of hypertension of renal vascular origin stated that "it is not usually recognized how severely a blood vessel must be constricted before appreciable fall in blood flow occurs, especially when blood pressure increases concurrently". From the above studies on blood flow through an arterial stenosis one may conclude that severe constriction of the artery (about 80 to 90% reduction in luminal area) is necessary, under resting conditions, to reduce blood flow significantly.

Along with the effect on blood flow an arterial stenosis has also been noted to alter the blood pressure in the carotid, renal, iliac and aortic arteries. Under resting conditions in vivo there is little drop in mean arterial blood pressure across a stenosis until the stenosis reduced the cross-sectional area of the vessel by a "critical" amount of 80 to 90%.

The pressure drop across a lesion in the carotid artery is insig-

nificant unless the arterial stenosis is quite severe. In 1960 Crawford et al[13] measured the intra-arterial pressures of the carotid artery proximal and distal to stenoses at operation. They found no significant pressure drop for lesions producing 72% luminal area occlusion. In stenoses associated with significant pressure drop arteriographic evaluation showed 75 to 100% luminal area occlusion. This is about the same amount of occlusion necessary to reduce blood flow in the carotid artery significantly.[1,2,3,4]

The effects of stenoses on the blood pressure in the renal and iliac arteries have also been studied. In 1962 Haimovici and Zinicola[14] placed a graded extraluminal constriction on the left renal artery of the dog (the right served as control) near its aortic origin. Acute graduated stenosis of the renal artery disclosed that no changes in blood pressure occurred up to a 84% cross-sectional area reduction of the arterial lumen. Between 84% and 91% a sudden marked change took place. Therefore, a critical stenosing zone existed just beyond 84% cross-sectional reduction. In 1963 May et al[9,10] showed that the pressure drop across a stenosis placed on the canine iliac artery did not begin to increase in magnitude until the stenosis reached 80%.

The effect of a stenosis on the arterial blood pressure of the aorta has been shown to be minor unless the constriction is very severe. In 1954 Haimovici[15] showed that a reduction of up to 84% of the area of the aorta induced insignificant blood pressure changes. A reduction of the area of the lumen between 84% and 91% resulted in significant pressure changes. When the stenosis reduced the area of the lumen by 91%, however, a critical stage was reached beyond

which any further decrease in the lumen caused sharp reduction in the mean pressure, thereby causing a haemodynamic state leading to a severe degree of arterial insufficiency. In 1956 Haimovici and Escher[6] presented data of the intra-arterial pressure changes associated with aortoiliac stenosis which showed that significant pressure reduction occurred only with marked constrictions in the order of 97% luminal area occlusion. In 1969 Koikkalainen and Luosta[16] measured the critical arterial stenosis of the distal abdominal aorta in rabbits. A silk thread was drawn, by a micrometer, progressively tighter about the artery by 0.1 mm increments down to the point where the pressure distal to the constriction dropped by 10 mm Hg. The mean critical arterial stenosis in normal conditions was 80% (reduction in luminal area). In 1969 Kindt and Youman[8] found that using a stricture of short length on the dog abdominal aorta that a significant decrease in pressure does not occur until a stricture of 91% or more in area is reached. Therefore, most of the studies above show that for the aorta the cross-sectional area must be reduced by at least 90% before there is a significant pressure drop across the stenosis. This is the same reduction required to reduce blood flow in the aorta.[5,7,8]

From the above studies on pressure drop across an arterial stenosis one may conclude that, as with the effect on blood flow, severe constriction of the artery (about 80 to 90% reduction in luminal area) is necessary under resting conditions to drop the pressure distal to the stenosis significantly.

Apart from the effect of the degree of constriction brought about by the stenosis, that of the shape, number and sequence of stenoses have been investigated. These have shown that such modifications

of stenoses effect the blood flow and pressure drop to only a minor degree. In 1964 Vondruden et al[2] used the dog carotid artery and found that if a second stenosis was added it only reduced the flow by 5 to 8%. Furthermore, the sequence of two unequal stenoses had no effect on total flow, i.e., removal of the larger caliber stenosis resulted in only neglible improvement in blood flow. In 1967 Robbins and Bentov[17] studied the kinetics of viscous flow in a model vessel and discovered that the shape did not play a critical role because the difference between the "worst" (sharp inlet and outlet margins) and the "best" (venturi) was in the order of 20%.

The length of a stenosis does not significantly effect the blood pressure and flow unless the constriction produced by the stenosis is near "critical" (i.e. produces a 80% or more reduction in luminal area) or the length is very long. In 1963 May et al[10] observed that the effect of a four-fold increase in the length of an average stenosis of 82% placed on the canine aorto-iliac arterial segment was to reduce the flow an average of 24.8%. In 1964 Vondruden et al[2] used the dog carotid artery and found that if the length of the stenosis was doubled it only reduced the blood flow by 5 to 8%. A series of experiments performed by Byar et al[18] in 1956 on an arbitrary model showed that a five-fold increase in length of a 1 mm diameter stenosis decreased flow to only 60% of its former value. In 1967 Edward[19] also found that a progressive increase in the length of the stenosis failed to give a proportionate drop in flow, owing to the tendancy for the increase in length of the stenosis to diminish turbulence.

A model study by Robbins and Bentov[17] showed that an increase in

length of the stenosis was without effect if the narrowing was not great. The length of the stenosis, however, had a rapidly increasing influence with increasing severity of narrowing (eg.) at 90% stenosis increasing the length from 5 to 20 mm almost halved the volume of flow. In 1969 Kindt and Youmans[8] undertook a study on the dog abdominal aorta to determine the influence of stricture length (1 mm to 8 cm) on arterial blood flow with all degrees of constriction. Blood flow was decreased by 50%, if a 96% area constriction were lengthened from 5 to 40 mm. For each degree of stenosis, however, a critical length of stenosis existed at which there was little effect on blood flow but any further increase in length of stenosis produced a profound effect on blood flow.

From the above studies on the length, shape, number and sequence of stenoses it can be surmised that the shape of the stenosis has little effect on the blood pressure and flow; neither does the number or sequence of stenoses. The length of the stenosis does not effect the blood pressure or flow if the constriction is not near critical (i.e. it does not decrease the luminal area by 80% or more); provided that the stricture is of relatively short length.

Evidence has been presented that under resting conditions in vivo little change in blood pressure or flow is caused until the cross-sectional area of the artery has been reduced by a "critical" amount of about 80%. Changes in the peripheral vascular resistance, however, will alter the level of "critical" stenosis. Fiddian[11] explained the variation of "critical" stenosis with the magnitude of the peripheral resistance as a simple function of any two-resistance (in series)

system. Byar[18] stated that increasing the stenosis does not have any appreciable effect until the resistance across it is a significant part of the total resistance (i.e. stenosis plus peripheral resistance) across the system. Along the same lines, Gregg[20] stated that the effectiveness of a given localized constriction in reducing blood flow may be small or large and will vary in inverse relation to the peripheral vascular bed. Likewise, Robbins and Bentov[17] stated that in the living patient the stenosis of an artery will be without effect until its resistance reaches a higher level than the peripheral resistance of the arteriolar and capillary bed. Also, Edwards[19] demonstrated that the effect of a stenosis on a major artery is greatly influenced by the degree of impairment of the distribution system of that artery. As the terminal resistance rose the pressure distal to the stenosis increased, thus diminishing the differential pressure across the stenosis.

The influence of peripheral resistance on the effect of a stenosis has been realized since 1944 when Shipley and Gregg[21] found that the degree of stenosis necessary to initiate significant flow and pressure reduction varied with the peripheral resistance. They stated that their findings reveal no justification for the contention that a rather marked degree of constriction is required to produce a significant reduction in flow through a vessel. In 1963 May et al[9] found that while in the resting dog it was necessary to reduce the luminal area by 80% before a significant reduction in arterial flow and pressure were observed ipsilateral sympathectomy increased the flow by 176% and reduced the critical stenosis to 75% and exercise of the limb increased the flow by 241% and reduced the critical stenosis to

60%.

In 1968 Thomas et al[22] studied the effects of various hemodynamic alterations of peripheral resistance on the pressure gradient and blood flow in a stenotic canine renal artery. Intravenously injected isoproterenol and blood loss decreased the pressure gradient and renal blood flow; but intra-arterially injected isoproterenol and reactive hyperemia increased them. They concluded that alterations in renovascular resistance tend to negate the value of the pressure gradient in a stenotic renal artery as a criterion for operative repair. In 1969 Koikkalainen and Luosta[16] found that the critical arterial stenosis in the rabbit distal abdominal aorta depended upon the peripheral vascular resistance. Successive ligation of the peripheral arteries increased the critical value of stenosis by degrees up to 100%. Administration of metarterenol (Aramine) had a similar effect. Following ischemia, however, the critical value of stenosis was reduced. In 1969 Kindt and Youmans[8] noted that the value of critical arterial stenosis of the dog abdominal aorta was reduced following the release of an arterial occlusion because the occlusion caused tissue hypoxia which lead to a decrease in peripheral resistance and an increase in flow rate.

In 1972 Carter[23] found that exercise in the limbs with mild arterial disease caused a profound fall in the ankle systolic pressure even though the pressure at rest was normal. He concluded that since exercise reduced peripheral resistance in exercising muscle, the blood flow through an area of stenosis increased leading to an increase in the pressure drop across the narrowing and to an abnormal fall in the distal pressure at the ankle.

The above evidence has shown that the effect of a given arterial stenosis will be dependant upon the peripheral vascular resistance. If the peripheral resistance is reduced so that the resistance caused by the stenosis is a significant part of the total resistance there will be a significant drop in blood pressure and flow caused by the stenosis. Therefore, the "critical" level of stenosis is dependent upon the magnitude of the peripheral resistance.

Besides its effects on blood pressure and flow an arterial stenosis has been noted to cause poststenotic dilation, i.e. an increase in the size of the artery downstream of a constriction. Initially poststenotic dilation was explained by a relative elevation of lateral pressure in the region downstream from the stenosis.[24,25] Investigators, however, could find no experimental or clinical evidence of a "local increase" of the lateral pressure in the poststenotic region - but rather a decrease.[26,27]

Poststenotic dilatation could not be explained by a "local increase" in lateral pressure downstream of the stenosis; so investigation was carried out to give another explanation - turbulence. In 1958 Spencer et al[28] demonstrated that murmurs of coarctation (congenital constriction of the aorta) are maximal in intensity in the region of poststenotic dilatation. In 1959 Bruns et al[3] hypothesized that vibration of the vessel walls (thrills) are of sufficient energy to cause structural fatigue and poststenotic dilatation. Roach[29,30,31] concluded that poststenotic dilatation develops in vivo only if and always if turbulence, as defined by the presence of a thrill and bruit, is present. In 1971 Boughner[32] and Robicsek[33] stated that the irregular turbulent motion of blood created by a constriction leads to damage

to the elastin component of the artery wall and poststenotic dilatation.

Pressure drop may effect the development of poststenotic dilatation. Hutchison[34] showed a decrease in the resonant frequencies of arterial wall vibration with reduced transmural pressure. This suggested that a pressure drop across a stenosis might cause resonant frequencies to decrease into the bandwidth of disturbance produced by turbulent blood flow. Thus in this way more vibration might be produced by pressure drop. From an in vivo study on adult dogs[29] Roach concluded that poststenotic dilatation occurs mainly or only with moderate stenoses with little or no pressure drop - at least measured by palpation at rest. Roach, however, did not take into consideration the activity of the dogs during the development of the dilation - thus with increased activity there may have been a greater pressure drop across the stenosis than suggested by examination of the dogs under anaesthesia. Thus, it was decided to examine in detail the pressure drop across minor stenoses and the effect of variation of downstream resistance.

SECTION I

Effect of Changes in Downstream Resistance on Pressures and Flow about Stenoses - Constant Pressure and Constant Flow Model Studies

INTRODUCTION

De Vries and Van den Berg[26], using rigid tubes, investigated the pressures upstream and downstream of a stenosis with variation of: the flow through the tube, the diameter of the stenosis, the value of the peripheral resistance and the level of mean pressure. Their experiments were performed with water as the perfusion fluid. The present experiments were performed with a bentonite solution as well as water to observe if changes in viscosity would alter the pressures obtained. Furthermore, De Vries and Van den Berg employed a metal diaphragm as their stenosis. It was felt that a 0.5 cm long stenosis with a 45° angle at each end would better simulate those stenoses found in arteries.

Shipley and Gregg[21] found that the degree of stenosis necessary to initiate significant flow and pressure reduction varied with the peripheral resistance. Their findings revealed no justification for the contention that a rather marked degree of constriction is required to produce significant reduction in flow through a vessel. The effect of peripheral resistance was re-investigated to discover what degree of constriction with what magnitude of downstream resistance produces significant pressure and flow reduction.

MATERIALS AND METHODS

For the constant pressure and constant flow model studies, four models of rigid acrylic tubing with an internal diameter of 0.6 cm were used. Inside each model was placed a 0.5 cm long stenosis, with a 45° angle at each end, 30 cm from the entrance end. The internal diameters of the stenoses were 0.1 cm, 0.2 cm, 0.3 cm and 0.4 cm; therefore, the areas were reduced 97%, 89%, 75% and 53% respectively. Six (or five) 19 guage needles were inserted into the model from the bottom to lie flush with the inside surface of the tubing. One was placed 4 cm upstream of the stenosis, one was placed at the stenosis (not present for the constant pressure experiments with water) and the other four were placed downstream of the stenosis at intervals of 1 cm (see figure 1A). These 19 guage needles were connected up to three Stratham P23Db pressure transducers by means of three-way stopcocks. The pressure transducers were in turn connected to a Beckman Dynograph Recorder Type 504D through type 9872 strain guage couplers.

Resistances were placed at the exit end of the model - 15 cm from the stenosis. Five resistances were used with internal diameters of 0.13 cm, 0.18 cm, 0.23 cm, 0.32 cm, and 0.64 cm. They were constructed of tygon tubing by placing one tube inside the other until the required resistance was made (see figure 1A). The last tube - the required resistance, was 10 cm long. Flow rate was measured by collection into a graduated cylinder.

The perfusion solutions employed were distilled water and 2.5% bentonite. The 2.5% bentonite solution was made by making suspensions of 25 gm of laboratory grade bentonite powder with one litre of

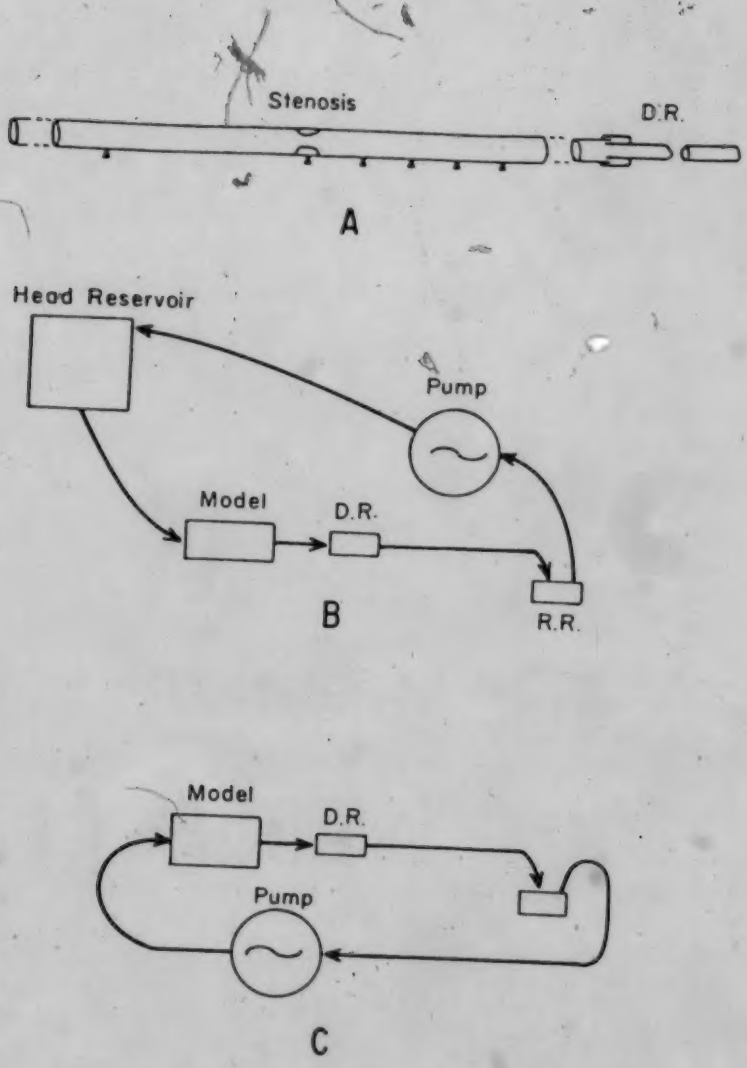

Figure 1: Schematic diagram of acrylic model (A), arrangement of apparatus for the constant pressure experiments (B) and the constant flow experiments (C).

distilled water. Fourteen litres of each perfusion solution was used and placed in a five gallon reservoir. The density of water and the 2.5% bentonite was 1 gm/cc at the temperature of the laboratory. The kinematic viscosity for the distilled water was 0.01 cm^2/sec (United States Bureau of Standards and The American Society for Testing Materials July 1, 1953). The kinematic viscosity of the bentonite solution was calculated by measuring the reflux time with a Cannon-Ubbelohde Viscometer #25 A237 which had a viscometer constant of 0.001882 centistrokes/sec. The kinematic viscosity for the 2.5% bentonite was 0.032 cm^2/sec. 2.5% bentonite was used because it is a particulate suspension and has a kinematic viscosity approximately equal to that of blood flowing in large blood vessels.

For the constant pressure experiments the pressure head consisted of a five gallon reservoir containing about 14 litres of the perfusion fluid. The reservoir was placed above the model of acrylic tubing so that the fluid level produced the appropriate pressure head equivalent. The distilled water level was 166 cm above the model to produce a pressure head equivalent of 122 mm Hg. The 2.5% bentonite solution levels were 160 cm and 202 cm to produce pressure head equivalents of 118 and 151 mm Hg respectively. Tubing with the same internal diameter as that of the model connected the reservoir to the model. The fluid flowed down this tubing from the head reservoir, through the model, then through the downstream resistance into a one gallon receiving reservoir. The fluid was pumped from the receiving reservoir to the head reservoir by means of a Harvard Apparatus Variable Speed Peristalic Pump #1215. The arrangement of the apparatus is seen in figure 1B.

The pump was kept at a high enough flow rate to maintain a near constant pressure head (i.e. fluid level in the head reservoir).

For the constant flow experiments the above pump was connected directly to the model rather than to the head reservoir (see figure 1C). The fluid flowed from the receiving reservoir, through the pump, through the model, then through the downstream resistance and into the receiving reservoir again. The flow was varied from 3 ml/sec to 20 ml/sec. Combinations with the smallest downstream resistance (ID = 0.13 cm) or with the 97% stenosis were not employed in the constant flow experiments because of the generation of very high pressures (above 225 mm Hg) even at the lowest pump setting.

RESULTS

A. Pressure Profiles - Constant Pressure Experiments

The pressure profiles of the constant pressure experiments using water and bentonite with a 53% stenosis are illustrated in Figure 2. The effect of changing the downstream resistance on the upstream and downstream pressures was similar in all three situations - water at 122 mm Hg. and bentonite at 118 and 151 mm Hg. It can be seen that with the greatest downstream resistance (ID = 0.13 cm) the upstream and downstream pressures remained within 6 mm Hg of the pressure heads. With the 0.13 and 0.18 cm downstream resistances there was little or no drop in pressure across the stenosis. As the downstream resistance, however, was decreased (i.e. with the 0.23, 0.32 and 0.64 cm resistances) there was an increase in flow accompanied by a decrease in upstream and downstream pressures and an increased pressure drop (as measured at a position 4 cm downstream).

When the 0.18 cm downstream resistance was employed with water as the perfusion fluid there was a marked pressure drop 1 cm downstream of the 53% stenosis but the pressure rose again very rapidly so that at a position 4 cm downstream the pressure drop had become very small. This phenomenon - a marked increase in the downstream pressure just downstream of the stenosis, was also observed with the 0.18 cm downstream resistance and with the 75% and 89% and to some extent with the 97% stenoses when water was the perfusion fluid. This unusual finding for the 0.18 cm resistance was not observed when bentonite was the perfusion solution employed or with any of the other resistances using water.

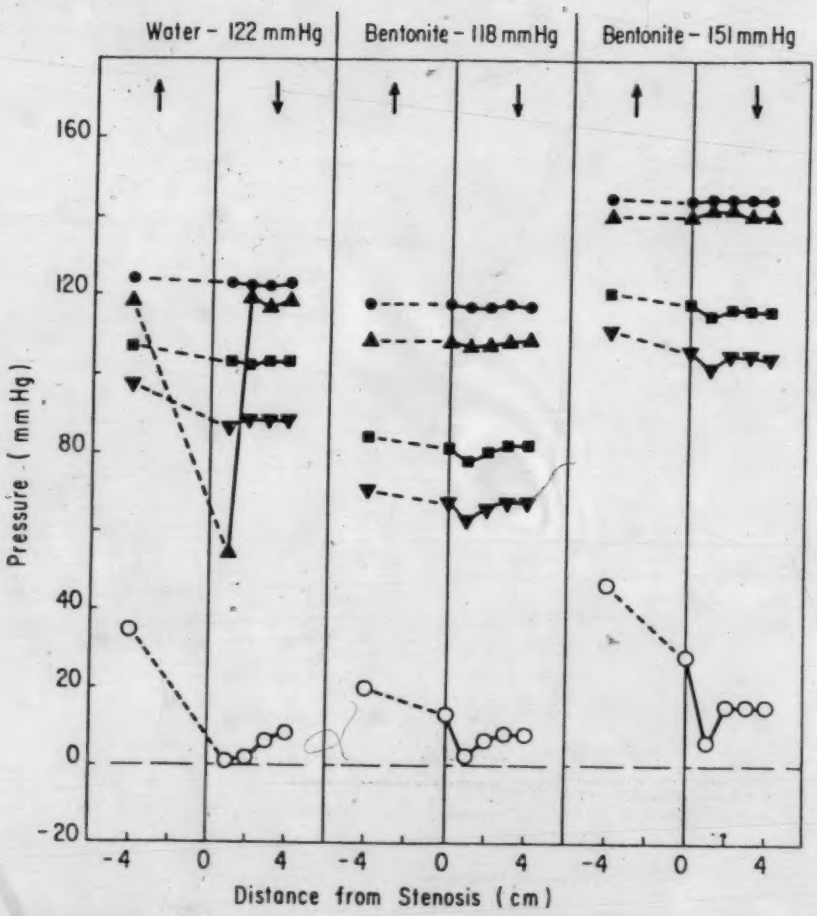

Figure 2: Pressure profiles across a 53% stenosis with constant pressure heads of 122 mm Hg using water and 118 mm Hg and 151 mm Hg using 2.5% bentonite solution.

Upstream region - ↑
Downstream region - ↓

ID = 0.13 cm resistance - ●
ID = 0.18 cm resistance - ▲
ID = 0.23 cm resistance - ■
ID = 0.32 cm resistance - ▼
ID = 0.64 cm resistance - ○

The pressure profiles of the constant pressure experiments using water and bentonite with a 75% stenosis are illustrated in Figure 3. It can be seen that a similar pattern to that found with the 53% stenosis was obtained but in any given case the pressure drop was greater. With the greatest downstream resistance (ID = 0.13 cm) there was little or no drop in pressure across the stenosis but as the downstream resistance was lessened there was an increase in flow accompanied by an increased pressure drop (as measured at a position 4 cm downstream).

The pressure profiles of the constant pressure experiments with water and bentonite with an 89% stenosis are illustrated in Figure 4. It can be seen that a similar pattern to that obtained with the 53% and 75% stenoses was obtained but in each case the pressure drop was greater. Thus the upstream pressures decreased and the flow increased as the downstream resistance was decreased. With the greatest downstream resistance (ID = 0.13 cm) there was a very small drop in pressure across the 89% stenosis. As the downstream resistance was lessened causing an increase in flow there was a greater pressure drop (as measured at a position 4 cm downstream) across the 89% stenosis. When the least narrow resistance (ID = 0.64 cm) was employed the pressure at the 89% stenosis and 1 cm downstream of it were subatmospheric and at these positions there were measurable pressure fluctuations. Further downstream the pressures did not increase substantially above atmospheric. When bentonite was the perfusion solution and the 0.23, 0.32 and 0.64 cm resistances were employed the minimal pressure occurred at the stenosis but it rose and stabilized within 3 cm downstream.

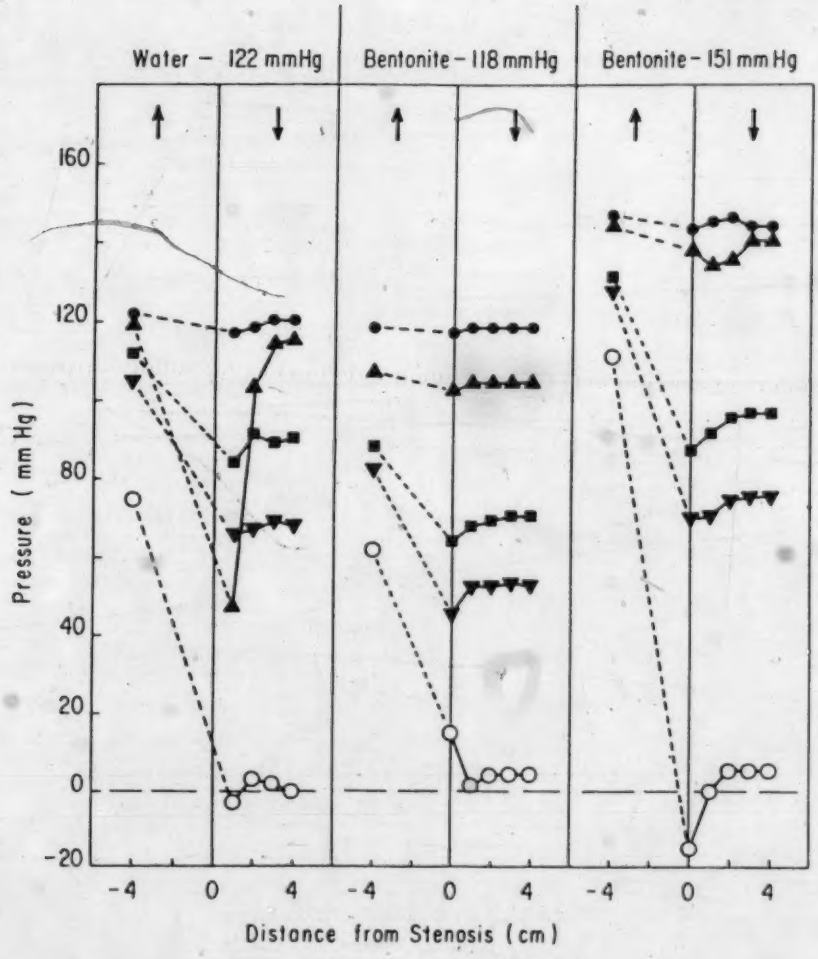

Figure 3: Pressure profiles across a 75% stenosis with constant pressure heads of 122 mm Hg using water and 118 mm Hg and 151 mm Hg using 2.5% bentonite solution.

Upstream region - ↑
Downstream region - ↓

ID = 0.13 cm resistance - ●
ID = 0.18 cm resistance - ▲
ID = 0.23 cm resistance - ■
ID = 0.32 cm resistance - ▼
ID = 0.64 cm resistance - o

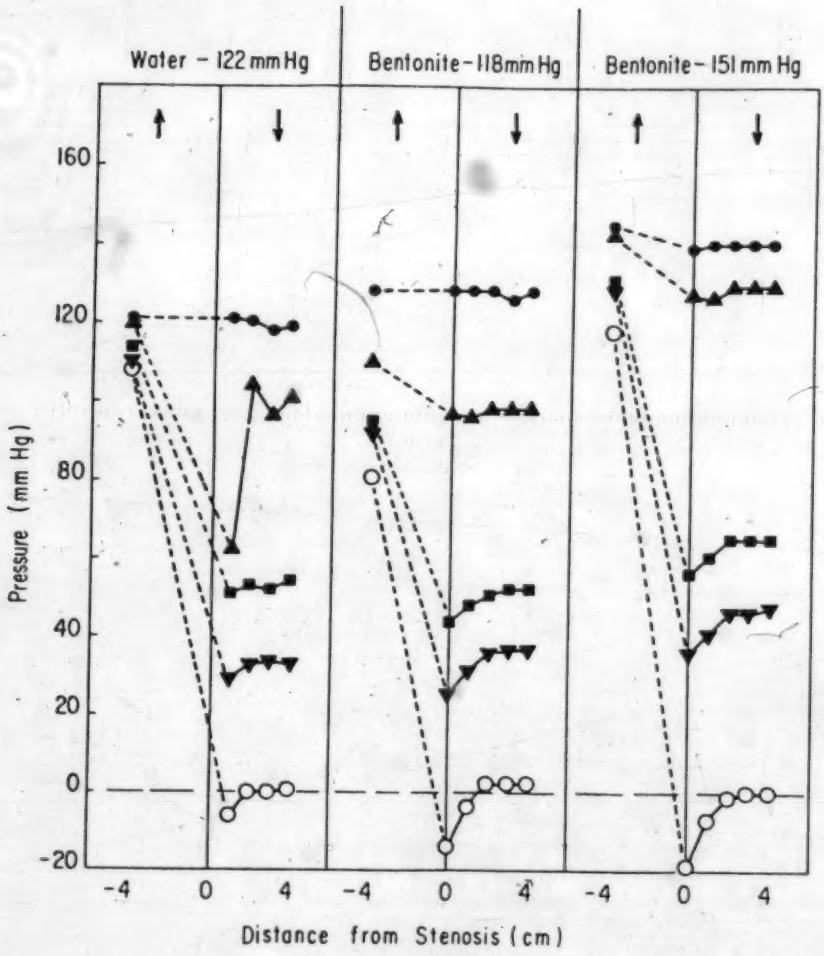

Figure 4: Pressure profiles across an 89% stenosis with constant pressure heads of 122 mm Hg using water and 118 mm Hg and 151 mm Hg using 2.5% bentonite solution.

Upstream region - ↑
Downstream region - ↓

ID = 0.13 cm resistance - ●
ID = 0.18 cm resistance - ▲
ID = 0.23 cm resistance - ■
ID = 0.32 cm resistance - ▼
ID = 0.64 cm resistance - ○

The pressure profiles of the constant pressure experiments with water and bentonite solution with a 97% stenosis are illustrated in Figure 5. It can be seen that a similar pattern to that obtained with the 53%, 75% and 89% stenoses was found but in each case the pressure drop was greater. With the 97% stenosis, however, the upstream pressure remained within 5 mm Hg of the pressure heads with all the downstream resistances employed instead of falling as the downstream resistance was decreased as it did with the 53%, 75% and 89% stenoses. Furthermore, there was always a pressure drop across the 97% stenosis no matter which downstream resistance was employed. With the 53%, 75% and 89% stenoses there was not a substantial pressure drop when the 0.13 cm resistance was employed. With the 97% stenosis as the downstream resistance was progressively decreased the pressure drop increased very rapidly at first but it approached a maximum with the 0.32 and 0.64 cm resistances because the pressure drop became nearly equal to the pressure head. With the 0.32 and 0.64 cm downstream resistances the pressures were zero or subatmospheric downstream of the 97% stenosis and with the 0.23 cm downstream resistance the pressures downstream were 6 mm Hg or less. When bentonite was the perfusion solution employed the pressures were within 1.5 mm Hg of each other at all positions downstream. Also the minimal pressures were always downstream of the stenosis not within it when bentonite was used. When water, however, was the perfusion solution employed the downstream pressures did not always quickly stabilize for there is a tendancy for the pressure to rise for the first 3 or 4 cm downstream.

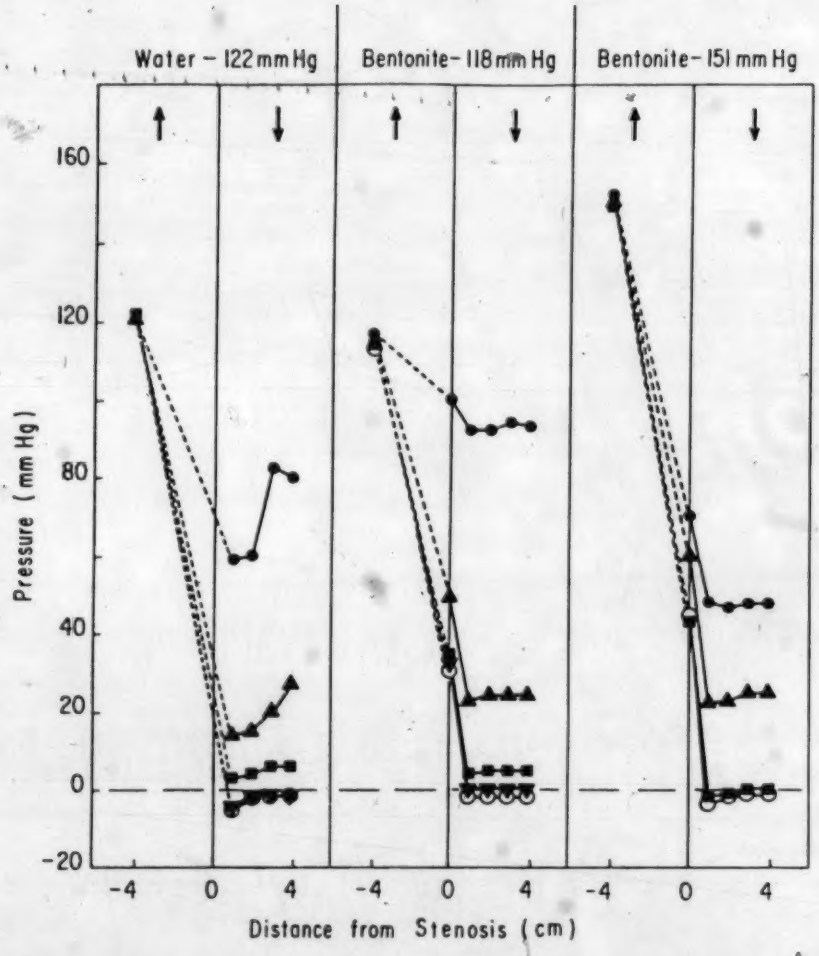

Figure 5: Pressure profiles across a 97% stenosis with constant pressure heads of 122 mm Hg using water and 118 mm Hg and 151 mm Hg using 2.5% bentonite solution.

Upstream region - ↑
Downstream region - ↓

ID = 0.13 cm resistance - ●
ID = 0.18 cm resistance - ▲
ID = 0.23 cm resistance - ■
ID = 0.32 cm resistance - ▼
ID = 0.64 cm resistance - ○

B. Pressure-Flow Characteristics - Constant Flow Experiments

Pressure profiles for the constant flow experiments were obtained which were similar to those of the constant pressure experiments. With the constant flow experiments, however, it was possible to vary the flow in consistent increments and thus obtain the pressure-flow characteristics for each stenosis and downstream resistance.

The effect of flow, percentage stenosis and downstream resistance for the constant flow experiments with bentonite as the perfusion solution is illustrated in Figure 6. When the lesser downstream resistances (ID = 0.23, 0.32 and 0.64 cm) were employed with any stenosis the flow needed to be increased to about 3 or 4 ml/sec before the upstream pressure increased above atmospheric.

There is a near linear relationship between upstream pressure and flow (mean correlation coefficient = 0.96, se = 0.02) for all the downstream resistances and stenoses (see Table I for correlation coefficients) - especially if the upstream pressure does not exceed 150 mm Hg. Once the upstream pressure exceeds 150 mm Hg there is a marked increase in the upstream pressure for a small increase in flow. In Figure 6 the slopes of the upstream pressure (in mm Hg) versus flow (in ml/sec) graphs will be the total resistance in arbitrary resistance units (ARU's), consisting of the stenosis resistance and the downstream resistance. The slopes are listed in Table I. For any given stenosis as the downstream resistance was increased there was an increase in the slopes of the pressure-flow graphs. Furthermore, for almost every downstream resistance as the percentage stenosis was increased there was an increase in the slope of the pressure-flow

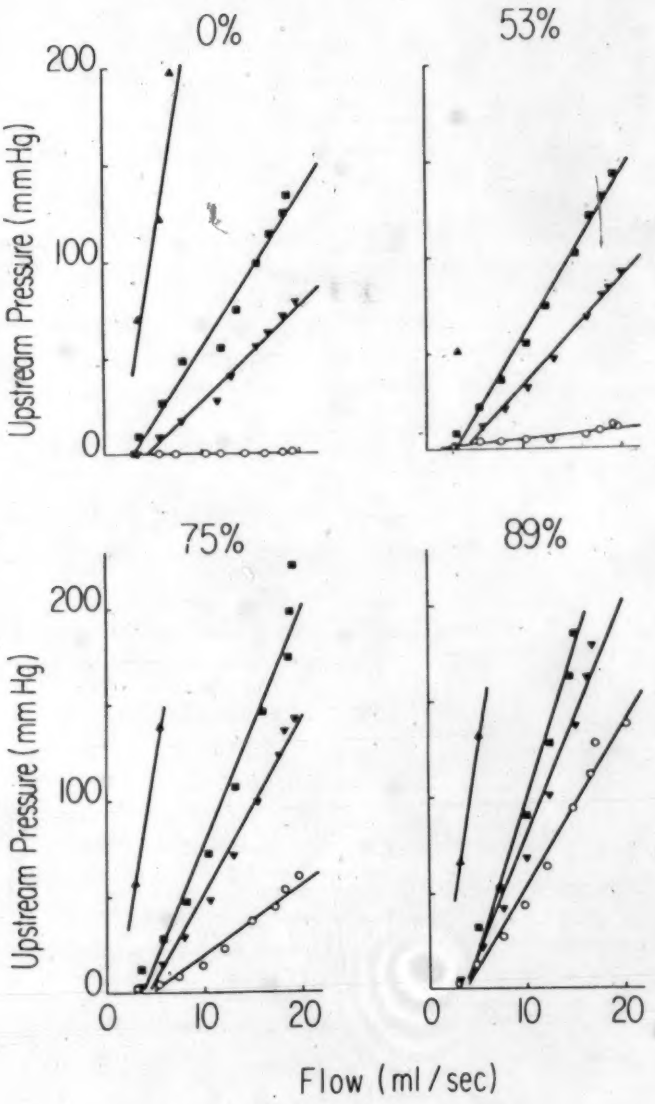

Figure 6: Effect of flow, percentage stenosis and downstream resistance on upstream pressure.

ID = 0.18 cm resistance - ▲
ID = 0.23 cm resistance - ■
ID = 0.32 cm resistance - ▼
ID = 0.64 cm resistance - ○

Table I: Slopes of Upstream Pressure versus Flow of Figure 6

% Stenosis	I.D. of Downstream Resistance (cm)	Slope ARU's	Cor. Coef.
0	0.18	35.5	0.95
	0.23	7.0	0.98
	0.32	4.9	0.99
	0.64	0.1	0.69
53	0.23	8.5	0.99
	0.32	5.5	0.99
	0.64	0.5	0.94
75	0.18	32.2	1.00
	0.23	12.6	0.98
	0.32	9.2	0.99
	0.64	3.6	0.98
89	0.18	32.8	1.00
	0.23	15.7	0.99
	0.32	12.8	0.99
	0.64	8.7	0.99

graphs. This does not appear to be true for the 0.18 cm resistance (the slope remains constant) suggesting that the stenosis resistance is very small in comparison to the resistance of this downstream resistance.

The effect of flow, percentage stenosis and downstream resistance on downstream pressure for the constant flow experiments with bentonite as the perfusion solution is illustrated in Figure 7. When the lowest downstream resistance (ID = 0.64 cm) was employed with any stenosis the downstream pressure never exceeded 4 mm Hg. When the two next lowest downstream resistances (ID = 0.32 and 0.23 cm) were employed with any stenosis the flow needed to be increased to about 3 or 4 ml/sec before the downstream pressures increased above atmospheric.

From Figure 7 it can be seen that there is a near linear relationship between downstream pressure and flow (mean correlation coefficient = 0.93, se = 0.04) for all the downstream resistances and stenoses. The correlation coefficients are listed in Table II. The slopes of the downstream pressure (in mm Hg) versus flow (in ml/sec) will be the downstream resistance in arbitrary resistance units (ARU's) - therefore there is little difference between the slopes no matter what the percentage stenosis. The slopes are listed in Table II and are about 30 to 35 ARU's, 8 ARU's, 5 ARU's and 0 ARU's for the downstream resistances 0.18, 0.23, 0.32 and 0.64 cm (ID's) respectively, and these are the respective resistances of the downstream resistances. If one takes the slopes of the downstream pressure versus flow graphs (i.e. the downstream resistance) and subtracts it from the slopes of the upstream pressure versus flow graphs (i.e. the total resistance - stenosis plus downstream resistance) one can obtain the stenosis resistace. The stenosis

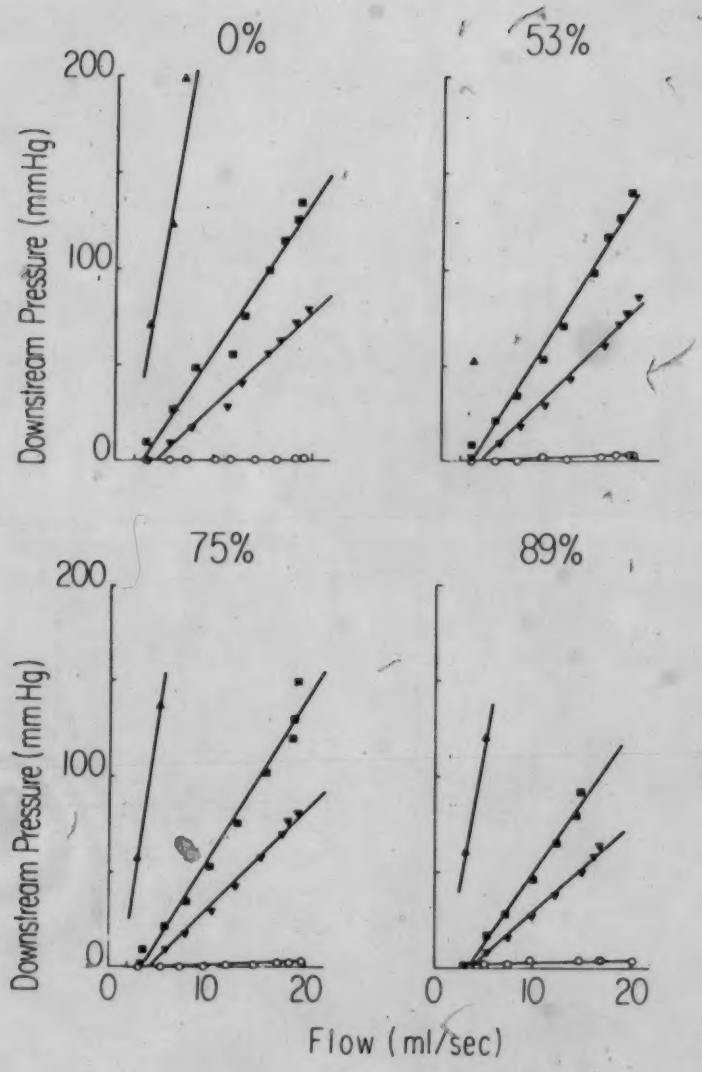

Figure 7: Effect of flow, percentage stenosis and downstream resistance on downstream pressure.

ID = 0.18 cm resistance - ▲
ID = 0.23 cm resistance - ■
ID = 0.32 cm resistance - ▼
ID = 0.64 cm resistance - o

Table II: Slopes of Downstream Pressure versus Flow of Figure 7

% Stenosis	I.D. of Downstream Resistance (cm)	Slope ARU's	Cor. Coef.
0	0.18	35.5	0.95
	0.23	7.9	0.98
	0.32	4.9	0.99
	0.64	0.1	0.69
53	0.23	8.3	0.99
	0.32	5.0	0.99
	0.64	0.2	0.95
75	0.18	31.8	1.00
	0.23	8.4	0.99
	0.32	5.1	0.99
	0.64	0.2	0.92
89	0.18	30.0	1.00
	0.23	7.6	0.99
	0.32	4.6	0.99
	0.64	0.1	0.50

resistances are about 0 ARU's, 0.5 ARU's, 4 ARU's and 8 ARU's for the 0%, 53%, 75% and 89% stenoses respectively. Hence, the resistance of the 0.18 cm downstream resistance is much greater than that of any stenosis employed.

C. Pressure Drop - Constant Pressure and Constant Flow Experiments

Pressure drop versus flow graphs were plotted for the constant pressure and constant flow experiments mentioned in sections A and B of the results. For the graphs in this section the different symbols represent the different types of experiments that were carried out (see figure legends). A decrease in the downstream resistance in the constant pressure experiments increased the flow rate which in turn increased the pressure drop across the stenosis. A decrease in downstream resistance in the constant flow experiments had no significant effect on the pressure drop across the stenosis. Therefore, a change in downstream resistance, for these experiments performed on acrylic models, had no significant effect on pressure drop that could not be accounted for by the change in flow rate.

The effect of flow on the pressure drop across the 53%, 75%, 89% and 97% stenoses is illustrated in Figure 8. For the 53% stenosis the pressure drop remains less than 5 mm Hg until the flow exceeds about 17 ml/sec. The maximum flow rate obtained was 47 ml/sec at which there was a maximum pressure drop of 30 mm Hg. The pressure drop across the 53% stenosis in all types of experiments increases linearly with increasing flow at a rate of 0.5 mm Hg/ml/sec or 0.5 ARU's - which

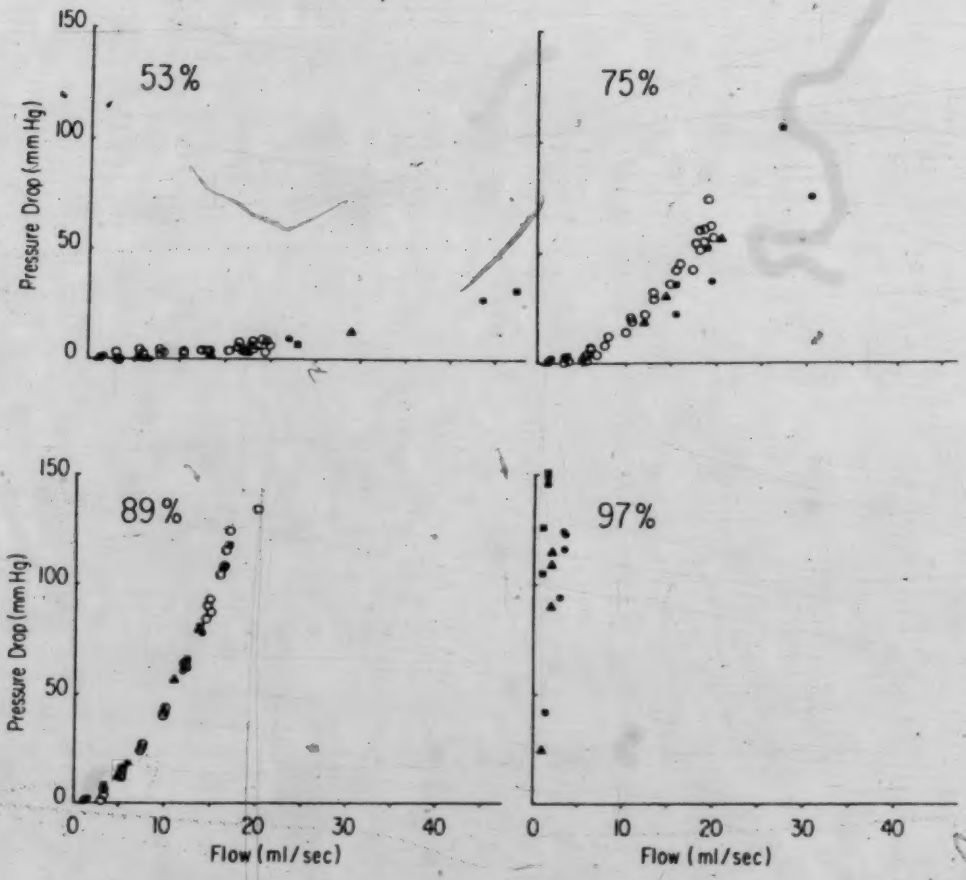

Figure 8: Effect of flow on pressure drop across 53%, 75%, 89% and 97% stenoses.

Water with 122 mm Hg head pressure - ●
Bentonite with 118 mm Hg head pressure - ▲
Bentonite with 151 mm Hg head pressure - ■
Bentonite with constant flow - o

is the value of the stenosis resistance obtained in section B.

With the 75% stenosis the pressure drop remains less than 5 mm Hg until the flow exceeds 6 ml/sec. This is about one-third the flow for a 5 mm Hg pressure drop across the 53% stenosis. The maximum flow rate was lower 30 versus 47 ml/sec and the maximum pressure drop was much greater 75 versus 30 mm Hg. The pressure drop across the 75% stenosis for the experiments with bentonite increased linearly with increasing flow up to 20 ml/sec at a rate of 4 mm Hg/ml/sec or 4 ARU's - which is the value of the stenosis resistance obtained in section B. Above 20 ml/sec there seems to be a slightly greater increase in pressure drop per flow increase for both the bentonite and the water experiments. For the experiments with water the rate of rise of pressure drop with flow was 2.6 mm Hg/ml/sec. This difference in the rate of rise of pressure drop with flow between bentonite and water was not readily apparent when the other stenoses were employed (i.e. 53%, 89% or 97%).

With the 89% stenosis the pressure drop remains less than 5 mm Hg only until the flow exceeds about 3 ml/sec. This is about one-half the flow for a 5 mm Hg pressure drop across the 75% stenosis and about one-sixth the flow for the same pressure drop across the 53% stenosis. In all types of experiments the maximum flow rate obtained for an 89% stenosis (17 ml/sec) was only about one-half that for a 75% stenosis (30 ml/sec) and about one-third that for a 53% stenosis (43 ml/sec). Furthermore, the maximum pressure drop obtained was very much greater for the 89% stenosis (about 130 mm Hg) than for the 75% stenosis (75 mm Hg) or the 53% stenosis (27 mm Hg). As the flow is increased from

5 to 15 ml/sec pressure drop increased at a rate of about 8 mm Hg per 1 ml/sec flow increase or 8 ARU's - the value of the stenosis resistance obtained in section B. Hence the rate of increase of pressure drop with flow increase or stenosis resistance, for an 89% stenosis is twice that for a 75% stenosis (i.e. 8 versus 4 ARU's) and about sixteen times that for a 53% stenosis (i.e. 8 versus 0.5 ARU's).

With the 97% stenosis no constant flow experiments were carried out because even at the lowest pump setting the combination of flow and resistance was such that the pressures exceeded 225 mm Hg. Thus Figure 8 gives results of the constant pressure experiments only for the 97% stenosis. For both water and bentonite the pressure drop exceeded 5 mm Hg even at the lowest flow rates of about 1 ml/sec. The maximum flow rate obtained with water was 3.6 ml/sec while that with bentonite was about 2 ml/sec. Therefore the maximum flow rates with the 97% stenosis were much less than that for the 89% (17 ml/sec), 75% (30 ml/sec) or 53% (43 ml/sec) stenosis. The maximum pressure drop across the 97% stenosis with the constant pressure experiments with water (124 mm Hg) or bentonite (115 and 151 mm Hg) was approximately equal to the pressure head. The rate of increase of pressure drop with flow increase is extremely rapid (in excess of 50 mm Hg/ml/sec or 50 ARU's) for the 97% stenosis; hence, the stenosis resistance was very much greater than the 89% (8 ARU's), 75% (4 ARU's) or 53% (0.5 ARU's) stenosis.

DISCUSSION

The constant pressure model experiments (figures 2, 3, 4 and 5) showed that with a decrease in the downstream resistance an increase in the pressure drop across the stenosis was observed. As the downstream resistance was decreased there was an increase in flow accompanied by a decrease in upstream and downstream pressures and an increased pressure drop across the stenoses (as measured at a position 4 cm downstream). The effect of changing the downstream resistance was similar in all situations, i.e., water at 122 mm Hg and bentonite at 118 and 151 mm Hg. The pattern was similar for every stenosis employed (i.e. 53%, 75%, 89% and 97%) but as the degree of stenosis was increased there was a greater pressure drop.

It was further shown that there may be a significant pressure drop across a stenosis which causes a reduction in cross-sectional area of slightly in excess of 50%; however, this is only achieved with very low downstream resistance. When the 53% stenosis was employed with the 0.13 and 0.18 cm downstream resistances (i.e. the tightest) there was no pressure drop across the stenosis when the 0.23 and 0.32 cm downstream resistances were employed very little drop in pressure across the stenosis occurred. When the least narrow downstream resistance (i.e. 0.64 cm), however, was employed there was an appreciable pressure drop (i.e. greater than 10 mm Hg and about 50% of the upstream pressure).

In their pressure profile De Vries and Van den Berg[26] showed that the lateral pressure immediately downstream of the stenosis

was lower than the pressure at some distance downstream (i.e. the immediate pressure drop was somewhat greater than the sustained one). The pressure profiles of the constant pressure experiments (see figures 2, 3, 4, and 5) did sometimes show a small rise in pressure further downstream but usually not as marked as that indicated by De Vries and Van den Berg. The abrupt nature of the very narrow metal diaphragm used as their stenosis probably caused more localized turbulence within the vicinity of the stenosis and thus accounted for the greater immediate pressure drop. A further factor may be that De Vries and Van den Berg employed water as the perfusion solution while in the constant pressure experiments bentonite was employed (as well as water). When bentonite was employed there was a tendancy for the pressure downstream to stabilize more quickly (i.e. less of a sequential rise in pressure downstream was recorded). This was especially marked with the severe stenosis (i.e. 97% - see figure 5). This was probably due to the higher viscosity (3.2 times greater) of the bentonite solution tending to diminish the turbulence caused by the stenosis.

For the constant pressure experiments with water as the perfusion solution an anomalous finding occurred when the 0.18 cm downstream resistance was employed with the 53%, 75% and 89% stenoses (see figures 2, 3 and 4). There was a marked drop in pressure 1 cm downstream of the stenosis but the pressure rose again very rapidly so that 4 cm downstream the downstream pressure was nearly equal to the upstream pressure. This unusual finding was not observed when bentonite was the perfusion solution or with any of the other downstream resistances using water. This phenomenon is

probably due to boundary layer separation immediately downstream of the stenosis when flow rates are at the transition between laminar and turbulent flow.

For the constant flow experiments, employing bentonite as the perfusion solution, upstream and downstream pressure increased linearly with flow if the downstream resistance and stenosis were kept constant. When the downstream resistance and the stenosis were kept constant while the flow was increased there occurred an increase in upstream pressure that was proportional to the total resistance - stenosis plus downstream resistance (see figure 6). When the downstream resistance was kept constant (with any degree of stenosis) while the flow was increased there occurred an increase in downstream pressure that was proportional to the downstream resistance (see figure 7).

There was no appreciable pressure drop across the stenosis until the resistance across the stenosis was a significant part of the total resistance (i.e. stenosis plus downstream resistance). As pointed out by Fiddian[35] the system behaved as two resistances in series. There was a pressure drop across the 53% stenosis (resistance = 0.5 ARU's) only with the 0.64 cm downstream resistance (resistance = 0 ARU's) (see figure 2). There was no pressure drop across the 75% stenosis (resistance = 4 ARU's) with the 0.18 cm downstream resistance (resistance = 30 to 35 ARU's), but there were significant pressure drops with the other downstream resistances (resistance = 8, 5 and 0 ARU's) (see figure 3). For the 89% stenosis (resistance = 8 ARU's) there begins to occur a small pressure drop with the 0.18 cm downstream resistance (resistance = 30 to 35 ARU's), but there were very marked pressure drops when the lesser downstream resistances were employed (see figure 4). Hence, it is the resistance of the stenosis

with respect to the total resistance that determines the degree of pressure drop across the stenosis.

A change in downstream resistance, in the constant pressure experiments, had no significant effect on pressure drop that could not be accounted for by the change in flow rate. Therefore, a decrease in downstream resistance, in the constant pressure experiments, only increased the pressure drop across the stenosis because it increased the flow rate. In the constant flow experiments, if the downstream resistance was changed but the flow rate was kept constant there was no increase in the pressure drop across the stenosis.

The pressure drop across a stenosis is relatively independant of the viscosity of the perfusion solution (at least if the viscosity does not exceed 0.032 cm^2/sec). Referring to figure 8 one can observe that generally the increase in pressure drop with flow was almost identical for the constant pressure experiments with water or bentonite and the constant flow experiments with bentonite. Although an increase in viscosity tends to increase drag (tending to increase the pressure drop across a stenosis) it also tends to diminish turbulence (tending to decrease the pressure drop across the stenosis) (Byar[18]). The pressure drop, therefore, is not proportional to the viscosity of the perfusion solution.

SECTION II

Effect of Changes in Vascular Resistance and Blood Flow on the Pressure Drop Across Minor Stenoses Placed on the Dog Thoracic Aorta.

INTRODUCTION

The results of the preceeding section suggest the possibility that a stenosis which produces little pressure drop under conditions of high downstream resistance may produce significant pressure reduction under conditions of lowered downstream resistance. This led to the investigation of the possibility that a minor stenosis, i.e. one that produces little pressure or flow reduction under control conditions, may become significant, i.e. produce significant pressure and flow reductions, under conditions which decrease the peripheral vascular resistance. Three vasodilator substances were employed (histamine, isoproterenol and acetylcholine) to simulate varying physiological conditions of decreased peripheral vascular resistance. These drugs were infused intra-arterially to eliminate as much as possible their cardiac effects and to maximize their peripheral vascular effects. The dog thoracic aorta was employed because: (1) the intercostal arteries could be used for pressure taps; (2) its internal diameter was similar to that of the acrylic model employed in the previous section and (3) it could simulate very readily the clinical phenomena of aortic coarctations. Three degrees of constriction (50%, 70% and 80% reduction in area) were employed in the first series using histamine as the vasodilator to determine which degree of stenosis would give a minimal drop in pressure. The results of the first series suggested that 70% was such a stenosis, therefore in the next two series (using isoproterenol and acetylcholine) a 70% stenosis was used with two drug doses. In the series with isoproterenol and

acetylcholine a second and larger drug dose was employed to see if any further increase in pressure drop could be obtained.

MATERIALS AND METHODS

Three series of experiments were carried out on nine mongrel dogs (weights 14.5 - 23.5 Kg), that is, three dogs in each series. The dogs were anaesthetized with sodium pentobarbital (Nembutal^{R}) (30 mg/Kg), anaesthesia was maintained by giving 3 mg nembutal when necessary for the duration of the experiments. Immediately after induction the trachea was intubated and a cannula was placed in the right cephalic vein of the forelimb for the administration of anaesthetic. The animals were respired with a Harvard respirometer.

A lateral thoracic incision was made between the fifth and sixth ribs. The fifth and sixth ribs were removed, the chest cage was spread apart by means of rib spreaders and the thoracic aorta and the third to the eighth intercostal arteries on the both sides were exposed by blunt dissection. The third to the eighth intercostal arteries on the left side were cannulated and those on the right side as well as the second and the ninth on both sides were tied off. The cannulas in the third to the seventh intercostal arteries were connected to five Statham pressure transducers (two model P23AA and three model P23Db) and recorded on five channels of a Beckman dynograph. See figure 9 for schematic illustration of preparation. Mean arterial pressure was calculated from these recordings (Systolic + 2 X Diastolic)/3). The cannula in the eighth intercostal artery was used to infuse drugs intra-arterially at the rate of 1 ml/min to the lower half of the body. A flow probe (A-5000 series transducer, Parks Electronic Laboratories) was placed upstream of the third intercostal artery and connected to a ultasonic flowmeter

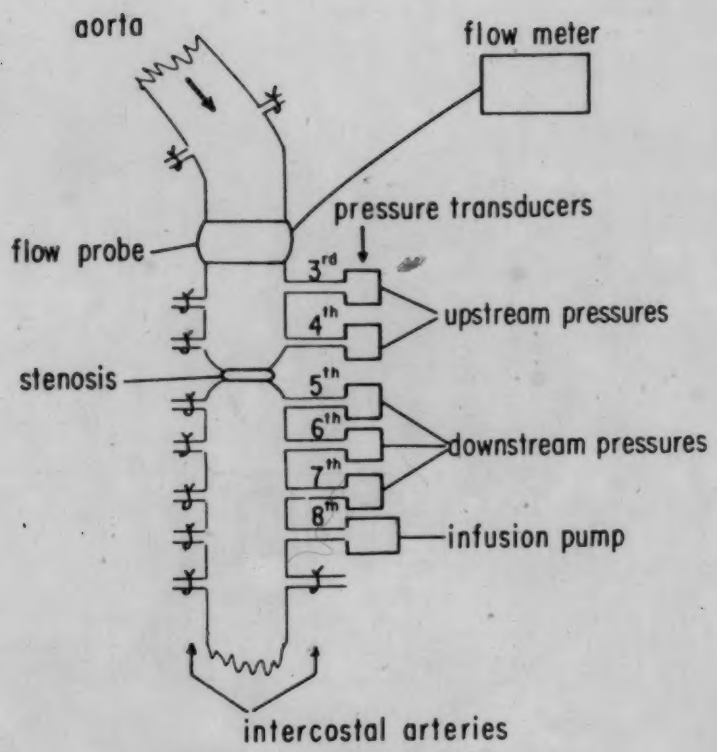

Figure 9: Schematic illustration of preparation for the experiments on the dog thoracic aorta in vivo.

(Doppler Flowmeter Model 803, Parks Electronic Laboratories) and this output was recorded simultaneously with the arterial pressures on the Beckman dynograph. The flowmeter was calibrated at the end of the experiment by timed collections from the aorta cannulated distal to the flow probe. Vascular resistance (in PRU's) was calculated by dividing mean arterial blood pressure (in mm Hg) by flow (in ml/sec). Minor stenoses were applied to the dog aorta between the fourth and fifth intercostal arteries. A calibrated externally variable 0.5 cm wide stenosis was used and the stenotic areas were then expressed as percent reduction of normal area, i.e. percent stenosis. Flow and downstream vascular resistance were varied by the intra-arterial infusions of either histamine (1 µg/Kg/min), isoproterenol (0.2 and 0.5 µg/Kg/min) or acetylcholine (0.5 and 1.0 µg/Kg/min) in the three series respectively under control conditions (i.e. no stenosis = 0%) and when minor stenoses were applied. 50%, 70% and 80% stenoses were employed in the experiments employing histamine. A 70% stenosis was employed in the experiments using isoproterenol and acetylcholine. Each drug infusion lasted fifteen minutes and was preceeded and followed by a fifteen minute infusion of saline (or 0.03% ascorbic acid in saline in the case of isoproterenol). The last five minutes of the infusions of the drug was compared with the last five minutes of the preceeding saline infusion.

RESULTS

A. Vasodilation by Infusions of Histamine

The results of the experiments using histamine on the dog thoracic aorta are illustrated in figure 10 and table III. It can be seen that the effect of histamine (1 μg/Kg/min) on the upstream pressure was similar with the 0%, 50%, 70% and 80% stenoses, that is, the average upstream pressure was decreased from about 110 to 95 mm Hg by the infusion of histamine. The effect of histamine (1 μg/Kg/min) on flow and downstream resistance was in opposite directions - as would be expected. Thus flow was increased and downstream resistance decreased.

During the infusion of saline constricting the dog thoracic aorta by up to 80% had no effect on the upstream pressure. Increasing degrees of constriction, however, decreased the flow, increased the downstream vascular resistance and increased the pressure drop. The decrease in flow was not significant for the 50% reduction (%ch = -9 ± 7, $p>0.05$) but it became significant when the aorta area was reduced by 70% (%ch = -18 ± 3, $p<0.05$) and highly significant when the stenosis was increased to 80% (%ch = -25 ± 2, $p<0.01$). The increase in downstream vascular resistance was not significant for a 50% (%ch = 12 ± 10, $p>0.05$) or a 70% (%ch = 23 ± 6, $p>0.05$) reduction in aorta area but was significant for an 80% stenosis (%ch = 29 ± 4, $p<0.05$). There was no pressure drop caused by the 50% stenosis (1 ± 1 mm Hg, $p>0.05$); a small one by the 70% stenosis (5 ± 2 mm Hg, $p>0.05$) and a moderate one by the 80% reduction in the area of the dog thoracic aorta

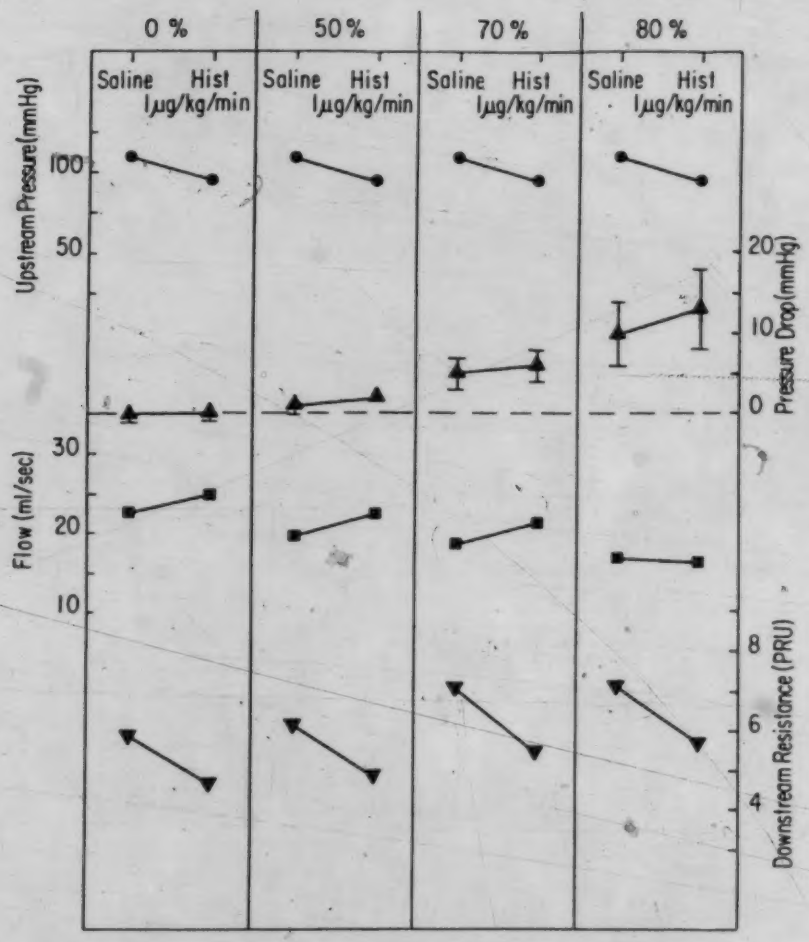

Figure 10: Effect of intra-arterial infusions of histamine on upstream pressure, pressure drop, flow and downstream vascular resistance under control conditions and with 50%, 70% and 80% stenoses applied to the dog thoracic aorta.

Table III - Effect of intra-arterial infusions of histamine on upstream pressure, pressure drop, flow and downstream vascular resistance under control conditions and with 50%, 70% and 80% stenoses applied to the dog thoracic aorta.

% Stenosis	Infusion	Upstream Pressure (mm Hg)	Pressure Drop (mm Hg)	Flow (ml/sec)	Downstream Resistance (PRU)
0	Saline	109	$0^{+}_{-}1$	22.5	5.9
	Hist.(1 µg/Kg/min)	95	$0^{+}_{-}1$	24.6	4.7
50	Saline	108	$1^{+}_{-}1$	19.6	6.2
	Hist.(1 µg/Kg/min)	97	$2^{+}_{-}0$	22.4	4.9
70	Saline	111	$5^{+}_{-}2$	18.6	7.5
	Hist.(1 µg/Kg/min)	96	$6^{+}_{-}2$	21.2	5.9
80	Saline	109	$10^{+}_{-}4$	16.7	7.9
	Hist.(1 µg/Kg/min)	95	$13^{+}_{-}5$	16.3	6.7

(10 ± 4 mm Hg, $p>0.05$).

With no stenosis (0%), histamine caused an increase in flow (22.5 to 24.5 ml/sec) but the increase was not significant (%ch = 9 ± 3, $p>0.05$). Downstream vascular resistance, however, was significantly decreased (5.9 to 4.7 PRU, %ch = -19 ± 3, $p<0.05$). There was no pressure drop during the saline or histamine infusions.

When the 50% stenosis was applied to the dog thoracic aorta the intra-arterial infusion of histamine (1 ug/Kg/min) caused a significant increase in the blood flow (19.6 to 22.6 ml/sec, %ch = 13 ± 2, $p<0.05$). There was a decrease in downstream resistance (6.2 to 4.9 PRU, %ch = -22 ± 6, $p>0.05$). A significant pressure drop was not recorded across the 50% stenosis either during the intra-arterial infusion of saline or histamine (1 ± 1 and 2 ± 0 mm Hg respectively).

With the 70% stenosis, histamine caused an increase in flow (18.6 to 21.6 ml/sec, %ch = 13 ± 5, $p>0.05$) and a significant decrease in downstream vascular resistance (7.1 to 5.5 PRU, %ch = -25 ± 5, $p<0.05$). The pressure drop was minor (5 ± 2 mm Hg) and was not significantly increased (6 ± 2 mm Hg) by histamine (ch = 1 ± 1 mm Hg, $p>0.05$).

Infusion of histamine caused no increase in flow (%ch = 1 ± 6, $p>0.05$) when an 80% stenosis was in place on the dog thoracic aorta. Downstream vascular resistance was decreased (7.9 to 6.7 PRU, %ch = -22 ± 6, $p>0.05$) and the pressure drop was increased from 10 ± 4 to 13 ± 5 mm Hg (ch = 3 ± 1 mm Hg, $p>0.05$); however, neither changes were significant.

The intra-arterial infusion of histamine (1 µg/Kg/min) under control conditions (0% stenosis) and with stenoses applied (50, 70 and 80%) generally caused an increase in the blood flow and a decrease in downstram vascular resistance. These changes, however, were not always significant. The histamine infusion tended to increase the pressure drop across the stenoses but the increases observed were very slight and not significant.

B. Vasodilation by Infusions of Isoproterenol

The results of the experiments using isoproterenol on the dog thoracic aorta are illustrated in figure 11 and table IV. It can be seen that the effect of isoproterenol (0.2 and 0.5 µg/Kg/min) was to decrease the upstream pressure, increase the flow, decrease the downstream vascular resistance and tend to increase the pressure drop across the 70% stenosis. It can also be observed that constricting the dog thoracic aorta by 70% increased the upstream pressure only slightly from 100 to 105 mm Hg. Further, the 70% stenosis had no significant effect on flow (%ch = -9 ± 11, $p>0.05$) or downstream vascular resistance (%ch = 13 ± 7, $p>0.05$). The pressure drop across the stenosis was minor (7 ± 3 mm Hg, $p>0.05$) during the infusion of saline.

With no stenosis (0%) isoproterenol (0.2 µg/Kg/min) caused a decrease in upstream pressure (ch = -15 mm Hg), an increase in blood flow (%ch = 8 ± 3, $p>0.05$) and a decrease in downstream vascular resistance (%ch = -32 ± 8, $p>0.05$). The larger dose (IPN 0.5 µg/Kg/min) caused a greater drop in upstream pressure (ch = -25 mm Hg) and

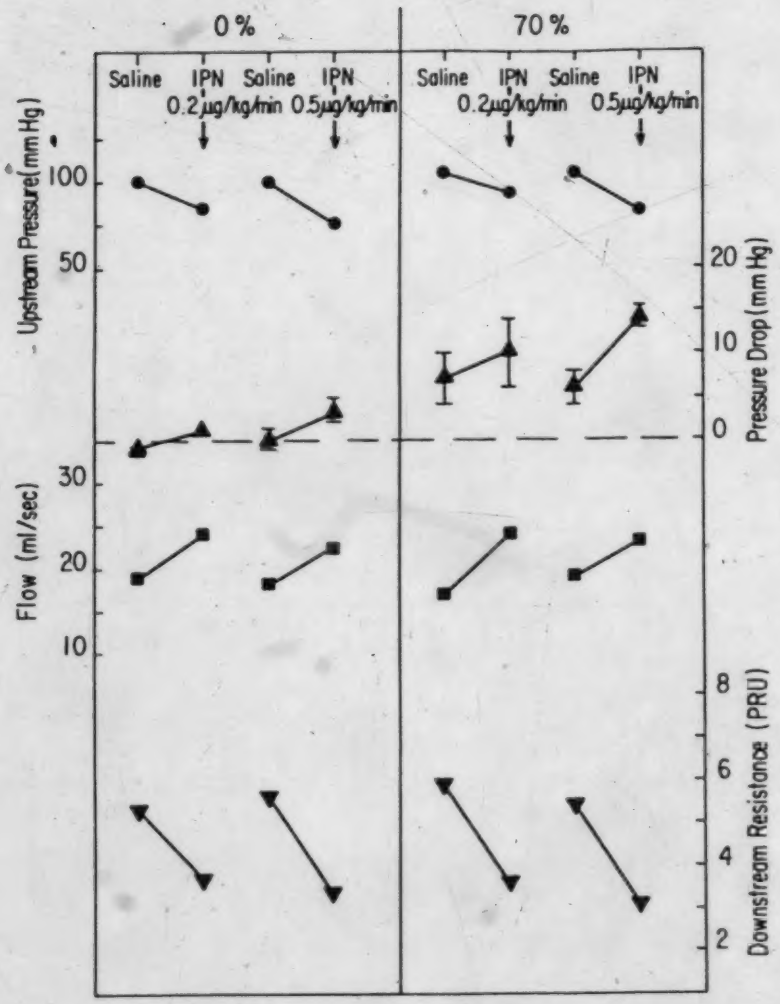

Figure 11: Effect of intra-arterial infusions of isoproterenol on upstream pressure, pressure drop, flow and downstream vascular resistance under control conditions and with a 70% stenosis applied to the dog thoracic aorta

Table IV - Effect of intra-arterial infusions of isoproterenol on upstream pressure, pressure drop, flow and downstream vascular resistance under control conditions and with a 70% stenosis applied to the dog thoracic aorta.

% Stenosis	Infusion	Upstream Pressure (mm Hg)	Pressure Drop (mm Hg)	Flow (ml/sec)	Downstream Resistance (PRU)
0	Saline	101	-1 ± 1	18.9	5.2
	IPN (0.2 µg/Kg/min)	86	1 ± 1	23.9	3.7
	Saline	99	0 ± 1	18.1	5.6
	IPN (0.5 µg/Kg/min)	77	3 ± 1	22.2	3.5
70	Saline	104	7 ± 3	16.8	6.3
	IPN (0.2 µg/Kg/min)	93	10 ± 4	23.8	4.1
	Saline	106	6 ± 2	18.9	5.7
	IPN (0.5 µg/Kg/min)	83	14 ± 1	23.1	3.7

increase in blood flow (%ch = 25±24, $p>0.05$) and a very significant decrease in downstream vascular resistance (%ch = -40±4, $p<0.01$). There was no pressure drop with no stenosis applied to the dog thoracic aorta.

With a 70% stenosis applied, the intra-arterial infusion of isoproterenol (0.2 µg/Kg/min) caused a decrease in upstream pressure (ch = -10 mm Hg), an increase in blood flow (%ch = 41±19, $p>0.05$) and a significant decrease in downstream vascular resistance (%ch = -38±6, $p<0.05$). The larger dose (IPN 0.5 µg/Kg/min) caused a greater drop in upstream pressure (ch = -20 mm Hg) but the increase in blood flow was less (%ch = 23±8, $p>0.05$) than that caused by the smaller dose. The decrease in downstream vascular resistance caused by the larger dose was significant (%ch = -42±7, $p<0.05$) and somewhat greater than that caused by the lower dose.

The smaller dose of isoproterenol (0.2 µg/Kg/min) caused a slight increase in pressure drop across the 70% stenosis from 7±3 to 10±4 mm Hg (ch = 3±1 mm Hg, $p>0.05$). The larger dose (IPN 0.5 µg/Kg/min), however, caused a significant increase in the pressure drop from 6±2 to 14±1 mm Hg (ch = 8±2 mm Hg, $p<0.05$). Therefore, for the 70% stenosis, the smaller dose of isoproterenol (0.2 µg/Kg/min) caused a greater increase in blood flow (41% vs 23%) but less of a decrease in downstream vascular resistance (-38% vs -42%) than the larger dose (IPN 0.5 µg/Kg/min). Furthermore, the increase in the pressure drop was greater for the larger dose (i.e. 8 vs 3 mm Hg).

C. Vasodilation by Infusion of Acetylcholine

The results of the experiments using acetylcholine on the dog thoracic aorta are illustrated in figure 12 and table V. It can be observed that, as in the first two series, constricting the area of the thoracic aorta by 70% had no effect on upstream pressure. The 70% stenosis caused no significant decrease in blood flow (%ch = -11 ± 3, $p>0.05$) or change in downstream vascular resistance (%ch = 0 ± 12, $p>0.05$). The 70% stenosis caused only a minor, though significant, pressure drop of 8 ± 1 mm Hg ($p<0.05$). It can further be seen that the effect of acetylcholine (0.5 and 1.0 µg/Kg/min) was to decrease the upstream pressure, increase the blood flow, decrease the downstream vascular resistance and increase the pressure drop across the 70% stenosis; and that these effects were generally greater at the larger dose.

With no stenosis applied to the dog thoracic aorta (0%) the smaller dose of acetylcholine (0.5 µg/Kg/min) caused a decrease in upstream pressure (ch = -15 mm Hg), a significant increase in blood flow (%ch = 22 ± 6, $p<0.05$) and a significant decrease in downstream vascular resistance (%ch = -30 ± 4, $p<0.05$). The larger dose (Ach 1.0 µg/Kg/min) caused the same decrease in upstream pressure as the lower dose (i.e. ch = -15 mm Hg), a slightly greater increment in blood flow (%ch = 25 ± 7, $p<0.05$) and a slightly greater decrease in downstream vascular resistance (%ch = -33 ± 5, $p<0.05$). The increase in blood flow were significant at both doses of acetylcholine as were the decreases in downstream vascular resistances. There was no pressure drop with no stenosis applied.

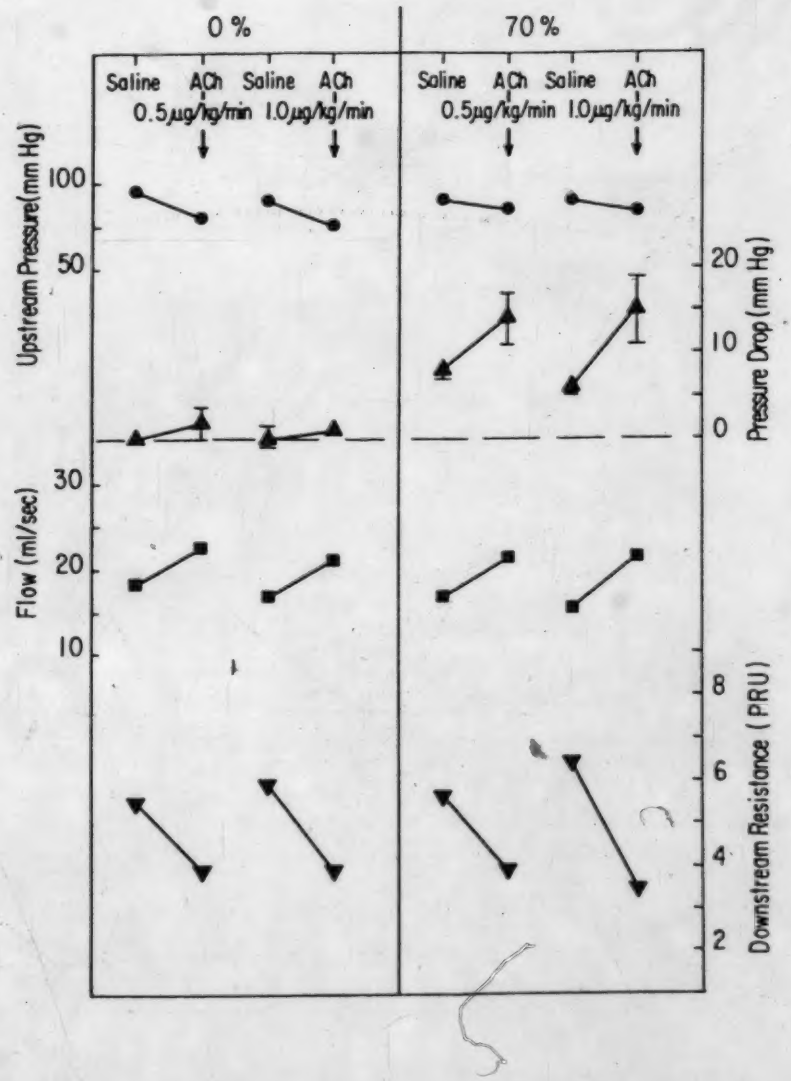

Figure 12: Effect of intra-arterial infusions of acetylcholine on upstream pressure, pressure drop, flow and downstream vascular resistance under control conditions and with a 70% stenosis applied to the dog thoracic aorta.

Table V - Effect of intra-arterial infusions of acetylcholine on upstream pressure, pressure drop, flow and downstream vascular resistance under control conditions and with a 70% stenosis applied to the dog thoracic aorta.

% Stenosis	Infusion	Upstream Pressure (mm Hg)	Pressure Drop (mm Hg)	Flow (ml/sec)	Downstream Resistance (PRU)
0	Saline	94	0 ± 0	18.3	5.5
	Ach (0.5 µg/Kg/min)	81	2 ± 2	22.4	4.0
	Saline	89	0 ± 1	16.7	5.9
	Ach (1.0 µg/Kg/min)	75	1 ± 1	20.8	4.0
70	Saline	90	8 ± 1	16.4	6.1
	Ach (0.5 µg/Kg/min)	84	14 ± 3	20.9	4.6
	Saline	89	6 ± 1	15.1	6.9
	Ach (1.0 µg/Kg/min)	78	15 ± 4	21.3	4.3

With a 70% stenosis applied the intra-arterial infusion of acetylcholine (0.5 µg/Kg/min) caused a decrease in upstream pressure (ch = -5 mm Hg), an increase in blood flow (%ch = 25±8, $p<0.05$) and a very significant decrease in downstream vascular resistance (%ch = -29±1, $p<0.005$). The larger dose (Ach 1.0 µg/Kg/min) caused a greater decrease in upstream pressure (ch = -10 mm Hg), a significant increase in blood flow (%ch = 40±9, $p<0.05$) and a very significant decrease in downstream vascular resistance (%ch = -45±3, $p<0.01$). The effects on blood flow and downstream vascular resistance were greater with the larger dose of acetylcholine.

The pressure drop across the 70% stenosis was significantly increased with the intra-arterial infusion of the smaller dose of acetylcholine (0.5 µg/Kg/min) from 8±1 to 14±3 mm Hg (ch = 6±1 mm Hg, $p<0.05$). The larger dose (Ach 1.0 µg/Kg/min) caused a greater increase in pressure drop from 6±1 to 15±4 mm Hg (ch = 9±3 mm Hg, $p>0.05$), though the result was not statistically significant.

DISCUSSION

These experiments show that when stenoses are applied to the dog thoracic aorta, during the infusion of saline, there is no pressure drop across a 50% stenosis (histamine experiments 1 ± 1 mm Hg), a minimal one across the 70% stenosis (histamine experiments 5 ± 2 mm Hg, isoproterenol experiments 7 ± 3 mm Hg and acetylcholine experiments 8 ± 1 mm Hg) and a moderate one across the 80% stenosis (histamine experiments 10 ± 4 mm Hg). Therefore, constricting the aorta by up to 80% in luminal area did not cause a significant pressure drop across the stenosis. This is in agreement with the results found by others[6,8,15], who found that with resting peripheral resistance marked constrictions of the aorta in the order of 84 to 97% luminal area occlusion were necessary to cause a significant pressure reduction.

During the infusion of saline, there was a nonsignificant decrease in blood flow caused by the 50% stenosis (histamine experiments $-9 \pm 7\%$), a small decrease by the 70% stenosis (histamine experiments $-18 \pm 3\%$, isoproterenol experiments $-9 \pm 11\%$, and acetylcholine experiments $-11 \pm 3\%$) and a moderate decrease by the 80% stenosis (histamine experiments $-25 \pm 2\%$). Therefore, constricting the aorta by up to 80% luminal area did not greatly reduce the blood flow. This is in agreement with the results of others[5,6.7,8], who found that with resting peripheral resistance very severe constrictions in the order of 82 to 94% were necessary before a significant decrease in blood flow occurs.

During the infusion of saline, there was no significant change in downstream resistance caused by a 50% stenosis (histamine experiments 12±10%), or a 70% stenosis (histamine experiments 23±6%, isoproterenol experiments 13±7% and acetylcholine experiments 0±12%) but it was moderately increased by an 80% stenosis (histamine experiments 29±4%). Others have not commented on the effect of a stenosis on downstream resistance aside from the statement that complete occlusion causes hypoxia and a decrease in downstream resistance[8]. The finding that there was no decrease in downstream resistance when the aorta was constricted by up to 80% in luminal area indicated that the stenosis was not severe enough to cause hypoxia that would have caused peripheral vasodilation. The reason for the moderate increase in downstream resistance with an 80% stenosis is obscure.

Constricting the dog thoracic aorta by up to 80% had no appreciable effect on the upstream pressure - therefore, these experiments may be considered essentially constant pressure. Hence one would expect, from the results of the constant pressure model experiments (section IA), a decrease in downstream (peripheral) resistance would cause an increase in flow, a decrease in upstream and downstream pressures and an increased pressure drop across the stenosis. Intra-arterial administration of histamine, isoproterenol and acetylcholine did cause a decrease in the downstream vascular resistance, an increase in blood flow, a decrease in upstream and downstream pressures and tended to increase the pressure drop across the stenosis. Others[9,16,21,22,23] have found that a decrease in peripheral resistance and an increase in blood flow increases the pressure drop

across a stenosis. The effect of changes in peripheral resistance on stenoses placed on the dog thoracic aorta in vivo, however, have not been studied before.

From the histamine experiments, it was discovered that there was no pressure drop across the 50% stenosis either during the intra-arterial infusion of saline or histamine ($1^{+}_{-}1$ and $2^{+}_{-}0$ mm Hg respectively). Therefore, a 50% stenosis is insignificant under control or reduced downstream vascular resistance. With a 70% stenosis the pressure drop was minor ($5^{+}_{-}2$ mm Hg) and was insignificantly increased by histamine. The 80% stenosis caused a pressure drop of $10^{+}_{-}4$ mm Hg which was increased slightly by histamine. From the histamine experiments it was concluded that the stenosis which gave a minimal pressure drop was 70%. Hence, 70% was a minor stenosis and it was the degree of stenosis used in the isoproterenol and acetylcholine experiments.

From the isoproterenol and acetylcholine experiments, in which two doses of the vasodilator substance were employed; it was found that the larger dose caused a greater decrease in downstream vascular resistance which usually caused a greater decrease in upstream pressure, increase in blood flow and pressure drop across the stenosis. This is in agreement with the results of others[8,9,11,16,17,18,20,21,22,23] that the effect of a given arterial stenosis will be dependant upon the peripheral vascular resistance. In these experiments only fairly small increases in blood flow and decreases in peripheral resistance were obtained (i.e. 20 to 40%). During physiological conditions such as exercise, however, the blood flow in the aorta can be increased to more than 200% and the peripheral resistance can be markedly reduced.

Therefore, if the physiological conditions of exercise could have been simulated one could anticipate much greater pressure drop across the minor stenosis.

SECTION III

Effect of Changes in Vascular Resistance on the Pressure Drops Across Minor Stenoses Placed on the Perfused Dog Ileo-Femoral Artery.

INTRODUCTION

The results of the preceeding section showed that vasodilation produces an increase in the pressure drop across a stenosis. The vasodilation, however, was achieved with an increase in the blood flow. It was not shown whether it was the decrease in downstream vascular resistance or the increase in blood flow that caused the increase in pressure drop across the stenosis. To separate the increase in flow rate from the decrease in downstream vascular resistance induced by the intra-arterial infusion of a vasodilator substance a third section employing a constant flow set-up was added - the perfused dog ileo-femoral artery. This enabled the blood flow to be held constant during the intra-arterial infusion of a vasodilator substance - acetylcholine.

The dog ileo-femoral artery was employed because: (1) it could be perfused without greatly effecting the general condition of the dog, (2) it could be isolated from other vascular connections and (3) upstream and downstream pressures could be readily monitored by arterial branches. Acetylcholine was chosen as the vasodilator substance because it is quickly broken down by the cholinesterases so that the vasodilation only occurred in the perfused limb. Stenoses with internal diameters of 2.44 mm, 2.26 mm, and 2.06 mm which reduced the arterial area by approximately 60%, 70% and 75% respectively were used in order that the stenoses employed were below critical. A second and larger dose of acetylcholine (0.5 vs 0.2 µg/Kg/min) was employed to see if any increase in pressure drop caused by the first dose could be enhanced by a further drop in peripheral vascular

resistance caused by the second larger dose.

MATERIALS AND METHODS

Experiments were performed on six mongrel dogs (weights 14 - 22.5 Kg). The animals were anaesthetised with sodium pentobarbital (Nembutal^{R}) (30 mg/Kg) and given 3 mg nembutal when necessary for the duration of the experiments. Immediately after induction the trachea was intubated and a cannula was placed in the right cephalic vein of the forelimb for the administration of anaesthetic. If necessary the animals were respirated with a Harvard respirometer. The left brachial artery (in two dogs) was cannulated to monitor systemic arterial pressure, which was measured with a Statham model P23AA pressure transducer.

The hind limb was perfused as follows. A midline abdominal incision was made and the dorsal aorta, the right and left iliac arteries, the caudal artery and the femoral profundus branch were exposed by blunt dissection. The lumbar arteries and small branches of the femoral artery were tied off to eliminate anastomotic blood flow. The animal was heparinized with an intravenous injection (5 mg/Kg). The caudal artery was cannulated to monitor upstream pressure. The femoral profundus branch was cannulated to monitor proximal downstream pressure. Another incision was made on the medial side of the right leg paralleling the femoral artery and the right femoral artery and a small branch about 5 cm distal to the femoral profundus branch were exposed by blunt dissection, and it was cannulated to monitor downstream pressure. The positions of these cannulas is shown in Figure 13. The above three cannulas were connected to three Statham P23Db pressure transducers and

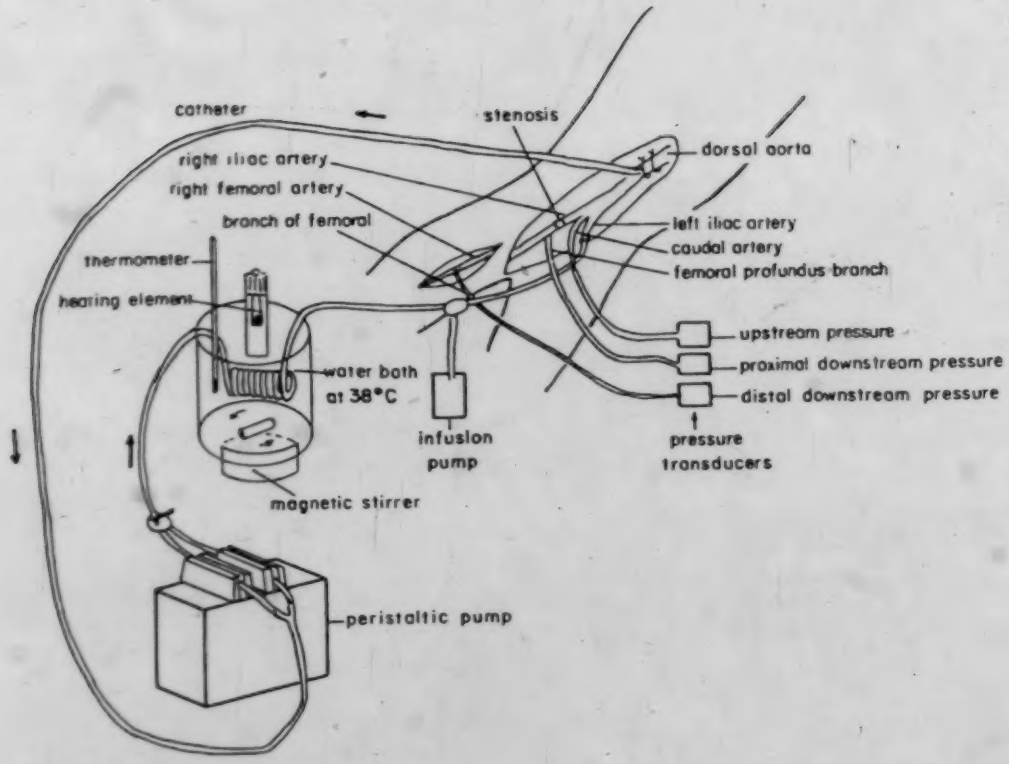

Figure 13: Illustration of preparation for the experiments on the perfused dog ileo-femoral artery.

recorded simultaneously on three channels of a Beckman dynograph. A cannula was inserted into the left iliac artery to return the blood to the right hind limb. Another cannula was inserted into the dorsal aorta and pushed well up into the aorta and tight ligatures were placed downstream around the aorta to eliminate anastomotic blood flow to the hind limb; this cannula was connected by means of a Y-tube to tygon tubing (2.5 mm ID) through which blood from the aorta was pumped with a Harvard Peristaltic pump through a thermostatically controlled water bath maintained at 38°C and back into the left iliac artery to perfuse the right limb. See figure 13 for set-up. The flow was adjusted so that the perfusion pressure approximated the systemic arterial pressure as recorded from the brachial artery. In those dogs in which systemic pressure was not monitored the flow was adjusted so that the perfusion pressure was approximately 100 mm Hg. Drugs were infused, at the rate of 1 ml/min, through a three-way connector just prior to where the blood entered the perfused limb. All the transducers were calibrated simultaneously with a mercury manometer at the beginning of the experiment, before application of each stenosis and at the end of the experiment.

An external stenosis one centimeter long was placed on the iliac artery one centimeter upstream of the femoral profundus artery. The internal diameters of the stenoses were 2.44 mm, 2.26 mm, and 2.06 mm; these reduced the arterial area by approximately 60%, 70% and 75% respectively. The 2.44 mm and 2.26 mm stenoses were placed on the iliac artery of five dogs. The 2.06 mm stenosis was placed on the iliac artery of four dogs. The blood flow was main-

tained at a constant rate for the control and each stenosis employed. For each stenosis as well as for the control five ten-minute drug infusions (at the rate of 1 ml/min) were performed: saline, acetylcholine 0.2 µg/Kg/min, saline, acetylcholine 0.5 µg/Kg/min, and saline. In each case the average pressures and resistances of the last five minutes of the infusions of acetylcholine were compared to the last five minutes of the preceeding saline infusion. Vascular resistance (in PRU's) was calculated by dividing the arterial pressure (in mm Hg) by the blood flow (in ml/min). The proximal pressure drop was taken to be the upstream pressure (as measured from the caudal artery) minus the proximal downstream pressure (as measured from the femoral profundus artery). The distal pressure drop was taken to be the upstream pressure minus the distal downstream pressure (as measured from the branch of the femoral artery 5 cm distal to the femoral profundus artery).

RESULTS

The results of the constant flow experiments on the dog ileo-femoral artery are illustrated in figure 14 and table VI. It can be seen that with progressively more severe stenoses the upstream pressure rose (no stenosis - 125 mm Hg, 2.44 mm (60%) - 160 mm Hg, 2.26 mm (70%) - 170 mm Hg, 2.06 mm (75%) - 185 mm Hg.) One effect of an intra-arterial infusion of acetylcholine (0.2 or 0.5 µg/Kg/min) was to decrease the upstream pressure by decreasing the vascular resistance because the flow was kept constant. Furthermore, the decrease in upstream pressure were greater at the larger dose.

The intra-arterial infusions of acetylcholine caused significant decreases in vascular resistance under control conditions and when stenoses were applied. Furthermore, the changes were greater at the larger dose. With no stenosis (control) acetylcholine caused very significant decreases in vascular resistance (Ach 0.2 µg/Kg/min, %ch = -35 ± 6, $p<0.005$; Ach 0.5 µg/Kg/min, %ch = -40 ± 6, $p<0.01$; $n=6$). With the 2.44 mm stenosis the decreases were also very significant (Ach 0.2 µg/Kg/min, %ch = -35 ± 2, $p<0.001$; Ach 0.5 µg/Kg/min, %ch = -46 ± 3, $p<0.001$; $n=5$). With the 2.26 mm stenosis the changes were very similar to those observed with the 2.44 mm stenosis (Ach 0.2 µg/Kg/min, %ch = -36 ± 3, $p<0.001$; Ach 0.5 µg/Kg/min, %ch = -42 ± 4, $p<0.001$; $n=5$). The decreases in vascular resistances were also significant with the 2.06 mm stenosis (Ach 0.2 µg/Kg/min, %ch = -27 ± 6, $p<0.05$; Ach 0.5 µg/Kg/min, %ch = -44 ± 3, $p<0.001$; $n=4$).

There were significant pressure drops across all stenoses

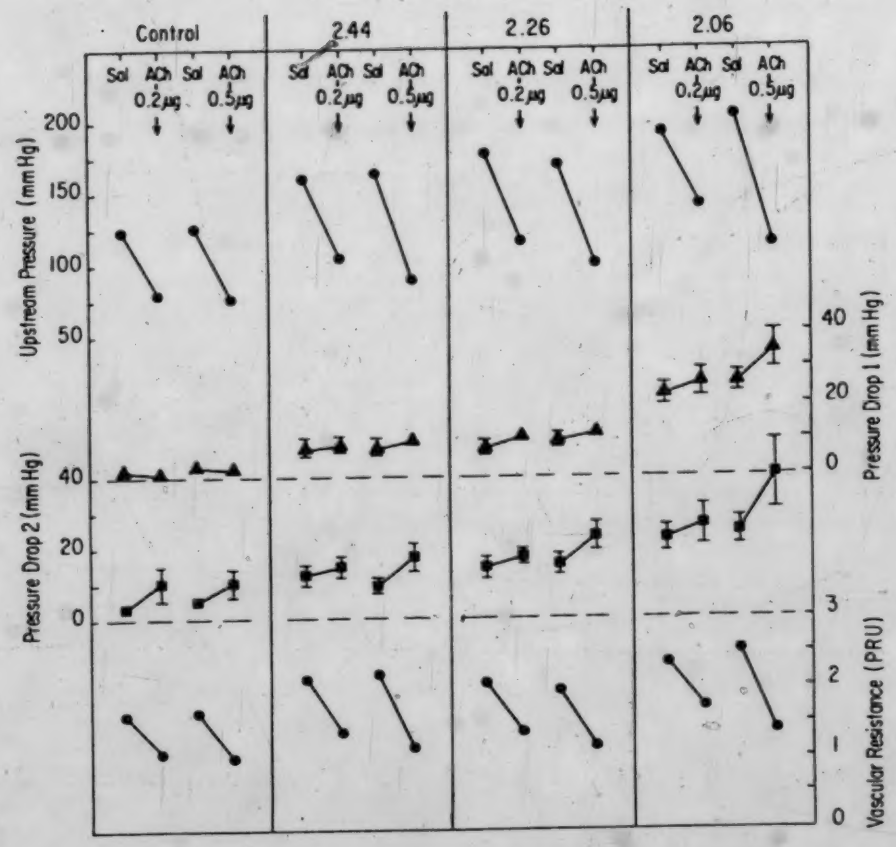

Figure 14: Response of the perfused dog hind limb to intra-arterial infusions of acetylcholine under control conditions and with stenoses applied.

Table VI - Response of the perfused dog hind limb to intra-arterial infusions of acetylcholine under control conditions and with stenoses applied.

Stenosis	Infusion	Upstream Pressure (mm Hg)	Pressure Drop 1 (mm Hg)	Pressure Drop 2 (mm Hg)	Vascular Resistance (PRU)
0%	Saline	123	2 ± 1	3 ± 1	1.63
	Ach (0.2 µg/Kg/min)	79	1 ± 1	10 ± 5	1.09
	Saline	126	3 ± 2	5 ± 1	1.66
	Ach (0.5 µg/Kg/min)	76	2 ± 1	10 ± 4	1.02
2.44 mm (60%)	Saline	160	8 ± 2	12 ± 3	2.12
	Ach (0.2 µg/Kg/min)	103	9 ± 2	14 ± 3	1.38
	Saline	163	8 ± 2	9 ± 2	2.19
	Ach (0.5 ug/Kg/min)	88	10 ± 1.5	17 ± 4	1.17
2.26 mm (70%)	Saline	176	8 ± 2	14 ± 3	2.06
	Ach (0.2 µg/Kg/min)	114	12 ± 1	17 ± 2	1.38
	Saline	168	9 ± 2	15 ± 3	1.96
	Ach (0.5 µg/Kg/min)	99	12 ± 1	23 ± 4	1.18
2.06 mm (80%)	Saline	189	23 ± 3	22 ± 4	2.35
	Ach (0.2 µg/Kg/min)	139	26 ± 4	26 ± 6	1.72
	Saline	202	26 ± 3	24 ± 4	2.52
	Ach (0.5 µg/kg/min)	112	35 ± 6	40 ± 10	1.39

both proximally (immediately downstream - as measured by the cannula in the femoral profundus branch) and distally (further downstream - as measured by the cannula in the small branch about 5 cm distal to the femoral profundus branch) during the initial saline infusions. The initial proximal (8 ± 2 mm Hg, $p<0.05$) pressure drop across the 2.44 mm stenosis was not significantly increased by either dose of acetylcholine (0.2 µg/Kg/min, 1 ± 1 mm Hg, $p>0.05$ and 0.5 µg/Kg/min, 2 ± 1 mm Hg, $p>0.05$). Likewise, neither was the initial distal (12 ± 3 mm Hg, $p<0.05$) pressure drop across the 2.44 mm stenosis (Ach 0.2 µg/Kg/min, 2 ± 1 mm Hg, $p>0.05$ and Ach 0.5 µg/Kg/min, 8 ± 3 mm Hg, $p>0.05$). With the 2.26 mm stenosis the initial proximal (8 ± 2 mm Hg, $p<0.05$) and distal (14 ± 3 mm Hg, $p<0.01$) pressure drops were slightly increased (3 ± 1 mm Hg) by the smaller dose (Ach 0.2 µg/Kg/min). The larger dose (Ach 0.5 µg/Kg/min) caused no significant increase in proximal pressure drop (2 ± 2 mm Hg, $p<0.05$) but a significant increase in distal pressure drop (8 ± 2.5 mm Hg, $p<0.05$). With the 2.06 mm stenosis the initial proximal (23 ± 3 mm Hg, $p<0.005$) and distal (23 ± 4 mm Hg, $p<0.01$) pressure drops were very significant. The smaller dose of acetylcholine (0.2 µg/Kg/min) caused no significant increase in proximal (3 ± 2 mm Hg, $p>0.05$) or distal (3.5 ± 2 mm Hg, $p>0.05$) pressure drops. The larger dose (Ach 0.5 µg/Kg/min) caused an increase in proximal (9 ± 4 mm Hg) and distal (15 ± 7 mm Hg) pressure drops but these increases were not significant at $p = 0.05$.

DISCUSSION

For the experiments on the perfused dog ileo-femoral artery, during the infusion of saline, there was a progressive rise in upstream blood pressure with progressively more severe stenoses. The Harvard Peristaltic pump was kept at a constant flow setting and therefore the perfusion pressure, i.e. upstream pressure, had to increase because the progressively more severe stenoses increased the resistance to flow; and $F = P/R$ (where F = flow, P = pressure and R = resistance).

For the experiments on the perfused dog hind limb, during the infusion of saline, there was a small pressure drop across the 2.44 mm stenosis (proximal, 8 ± 2 mm Hg, $p<0.05$; distal, 12 ± 3 mm Hg, $p<0.05$); a similar small pressure drop across the 2.26 mm stenosis (proximal, 8 ± 2 mm Hg, $p<0.05$; distal, 14 ± 3 mm Hg, $p<0.01$) but a larger pressure drop across the 2.06 mm stenosis (proximal, 23 ± 4 mm Hg, $p<0.005$; distal, 23 ± 4 mm Hg, $p<0.01$). Therefore, the 2.44 and 2.26 mm stenoses, which reduced the area of the lumen by approximately 60% and 70% respectively, are hemodynamically insignificant stenoses. The 2.06 mm stenosis (approximately 75% reduction in area) decreased the arterial pressure by 12%. These results are in agreement with those of May et al[9,10], who found that in the resting animal it was necessary to constrict the luminal area of the iliac artery by 80% before a significant 20% decrease in arterial pressure occurred. Therefore, all the stenoses employed were below critical.

In this section the flow was kept constant during all infusions,

therefore, if there were any changes in the pressures it was due to the change in downstream vascular resistance and not to a change in blood flow. The increases in pressure drops across the stenoses caused by the intra-arterial infusions of either dose of acetylcholine were very small in comparison to the significantly larger decreases in downstream resistance that resulted. This concurs with the constant flow model experiments of section I; that if the downstream resistance was changed but the flow rate was kept constant there was no increase in the pressure drop across the stenosis. Therefore, the increase in blood pressure drop across a stenosis elicited by changes in vascular resistances are accounted for by the changes in blood flow.

SUMMARY

The constant pressure model experiments showed that with a decrease in downstream resistance an increase in flow and an increase in the pressure drop across the stenosis was observed. The pattern was similar for every stenosis (i.e. 53%, 75%, 89% and 97%) but as the degree of stenosis was increased there was a greater pressure drop. It was further shown that with very low downstream resistance there may be a significant pressure drop across a 53% stenosis.

The constant flow model experiments showed that when the downstream resistance and the stenosis were kept constant while the flow was increased there occurred an increase in upstream pressure that was proportional to the total resistance - stenosis plus downstream resistance. When the downstream resistance was kept constant (with any degree of stenosis) while the flow was increased there occurred an increase in downstream pressure that was proportional to the downstream resistance.

From the model experiments it was shown that there was no appreciable pressure drop across the stenosis until the resistance across the stenosis was a significant part of the total resistance (i.e. stenosis plus downstream resistance). A decrease in the downstream resistance, in the constant pressure experiments, only increased the pressure drop across the stenosis due to the increased flow rate; because, in the constant flow experiments, if the downstream resistance was changed but the flow rate was kept constant there was no

increase in the pressure drop across the stenosis.

With resting peripheral resistance there was no pressure drop across a 50% stenosis, a minimal one across a 70% stenosis and a moderate one across a 80% stenosis applied to the dog thoracic aorta in vivo. A decrease in downstream (peripheral) resistance caused by the intra-arterial administration of vasodilator substances (histamine, isoproterenol or acetylcholine) increased the blood flow, decreased the upstream and downstream pressures and increased the pressure drop across the stenosis. A larger dose of vasodilator substance (isoproterenol or acetylcholine) caused a greater decrease in downstream resistance and a greater pressure drop across the minor (70%) stenosis. This showed that the effect of a given arterial stenosis will be dependant upon the peripheral vascular resistance.

For the experiments on the perfused dog hind limb (i.e. constant flow) with resting peripheral resistance (i.e. during saline infusion) minor stenoses (i.e. 60%, 70% and 75%) of the iliac artery caused a small (i.e. less than 12%) drop in arterial pressure. A decrease in downstream (peripheral) resistance caused by the intra-arterial administration of a vasodilator substance (acetylcholine) did not cause an increase in the pressure drop. It was concluded that the increase in blood pressure drop across a stenosis elicited by changes in vascular resistance are accounted for by changes in blood flow.

BIBLIOGRAPHY

1. Mann, F.C., Herrich, J.F., Essex H.E. and Baldes, E.J.: The effects of flow on the blood flow of decreasing the lumen of a blood vessel. Surgery 4 : 249, 1938.

2. Vondruden, W.J., Blaisdell, F.W., Hall, A.D. and Thomas, A.N.: Multiple arterial stenoses - effect on blood flow. Archives of Surgery 89 : 307, 1964.

3. Eklof, B. and Schwartz, S.E.: Critical Stenosis of the carotid artery in the dog. Scandinavian Journal of Clinical and Laboratory Investigation 25 : 349, 1970.

4. Youmans, J.R. and Kindt, G.W.: Influence of multiple vessel impairment on carotid blood flow in the monkey. Journal of Neurosurgery 29 : 135, 1968.

5. Wylie, E.J. and McGuinnes, J.S.: The recognition and treatment of arteriosclerotic stenosis of major arteries. Surgery, Gynecology and Obstetrics 97 : 425, 1953.

6. Haimovici, H. and Escher, D.J.W.: Aortoiliac stenosis - diagnosic significance of vascular hemodynamics, A.M.A. Archives of Surgery 72 : 107, 1956.

7. Schenk, W.G. Jr., Menno, A.D. and Martin, J.W.: Hemodynamics of experimental coarctation of the aorta. Annals of Surgery 53 : 163, 1961.

8. Kindt, G. and Youmans, J.R.: The effect of stricture length on critical arterial stenosis. Surgery, Gynecology and Obstetrics 128 : 729, 1969.

9. May, A.G., Van de Berg, L., DeWeese, J.A. and Rob, C.G.: Critical arterial stenosis. Surgery 54 : 250, 1963.

10. May, A.G., DeWeese, J.A. and Rob, C.G.: Hemodynamic effects of arterial stenosis. Surgery 53 : 513, 1963.

11. Van de Berg, L., DeWeese, J.A. and Rob, C.G.: The effect of arterial stenosis and sympathectomy on blood flow and the ergogram. Annals of Surgery 159 : 623, 1964.

12. Page, I.H., Dunstan, H.P. and Poutasse E.F.: Mechanism, diagnosis and treatment of hypertension of renal vascular origin. Annals of Internal Medicine 51 : 196, 1959.

13. Crawford, E.S., DeBakey, M.E., Blaisdell, F.W., Morris, G.C. Jr. and Fields, W.S.: Hemodynamic alterations in patients with cerebral arterial insufficiency before and after operation. Surgery 48 : 76, 1960.

14. Haimovici, H. and Zinicola, N.: Experimental renal artery stenosis - diagnostic significance of arterial hemodynamics. Journal of Cardiovascular Sugery, 3 : 259, 1962.

15. Haimovici, H.: Stenosing arterial thrombosis: an experimental physiopathologic study. Surgery 36 : 1075, 1954.

16. Koikkalainen, K. and Luosta, R.: A simplified method of measuring critical arterial stenosis. Annales Medicine Experimentalis et Biologiae 47 : 1, 1969.

17. Robbins, S.L. and Bentov, I.: The kinetics of viscous flow in a model vessel - effect of stenoses of various size, shape and length. Laboratory Investigation 16 : 864, 1967.

18. Byar, D., Fiddian, R.V., Quereau, M., Hobbs, J.T. and Edwards, E.A.: The fallacy of applying the Poiseuille equation to segmented arterial stenosis. American Heart Journal 70 : 216, 1965.

19. Edwards, E.A.: Dynamic consequences of arterial stenosis. Journal of Cardiovascular Surgery 8 : 386, 1967.

20. Gregg, D.E.: The Coronary Circulation in Health and Disease. Philadelphia, Lee and Febiger, 1950.

21. Shipley, R.E. and Gregg, D.E.: The effect of external constriction of a blood vessel on blood flow. American Journal of Physiology 141 : 289, 1944.

22. Thomas, C.G., Brackman, S.K. and Foster, J.H.: Variability of the pressure gradient in renal artery stenosis. Surgery, Gynecology and Obstetrics 126 : 339, 1968.

23. Carter, S.A.: Response of ankle systolic pressure to leg exercise in mild or questionable arterial disease. New England Journal of Medicine 287 : 578, 1972.

24. Campbell, M. and Kautze, R.: Congenital aortis valvular stenosis. British Heart Journal 15 : 179, 1953.

25. Holman E.: The obscure physiology of poststenotic dilation. Its relation to the development of aneurysms. Journal of Thoracic Surgery 28 : 109, 1954.

26. De Vries, H.K. and Van den Berg, L.: On the origin of poststenotic dilations. Cardiologia 33 : 195, 1958.

27. Robicsek, F., Sanger, P.W., Taylor, F.H., Magistra, R. and Foti, E.: Pathogenesis and significance of poststenotic dilation in great vessels. Annuals of Surgery 147 : 835, 1958.

28. Spenser, M.P., Johnston, F.R. and Meredith, J.H.: The origin and interpretation of murmurs in coarctation of the aorta. American Heart Journal 56 : 722, 1958.

29. Roach, M.R.: An experimental study of the production and time course of poststenotic dilation in the femoral and carotid arteries of adult dogs. Circulation Research 13 : 537, 1963.

30. Roach, M.R.: Changes in arterial distensibility as a cause of poststenotic dilation. The American Journal of Cardiology - Young Investigators' Award 11 : 802, 1963.

31. Roach, M.R. and Harvey, K.: Experimental investigation of poststenotic dilation. Canadian Journal of Physiology and Pharmacology 42 : 53, 1964.

32. Boughner, D.R. and Roach, M.R.: Effect of low frequency vibration on the arterial wall. Circulation Research 29 : 136, 1971.

33. Robischek, F., Tam, W., Daugherty, H.K. and Mullen, D.C.: The applicability of Bernoulli's law in the process of enlargement and rupture of aortic aneurysms. Journal of Thoracic Surgery 61 : 472, 1971.

34. Hutchison, K.J.: Effect of variation of transmural pressure on the frequency response of isolated segments of canine carotid arteries. Circulation Research 35 : 742, 1974.

35. Fiddian, R.V., Byar, D. and Edwards, E.A.: Factors affecting flow through a stenosed vessel. Archives of Surgery 88 : 83, 1964.